Giving the gold standard the cold shoulder
Delay to clozapine use in treatment-resistant schizophrenia

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GIVING THE GOLD STANDARD THE COLD SHOULDER:
DELAY TO CLOZAPINE USE IN TREATMENT-RESISTANT SCHIZOPHRENIA

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Abstract

Clozapine is the only antipsychotic that has been repeatedly shown to be effective in treatment-resistant schizophrenia. Despite this, it is underused. This thesis investigates prescribing patterns of clozapine in a large NHS Trust in South East London. Retrospective clinical note review found a mean theoretical delay to clozapine prescription of 3.93 years. The length of delay to clozapine use was not affected by age, ethnicity or diagnosis. In a survey of clinical staff, the majority were familiar with clozapine prescribing guidelines and how to prescribe the drug, and felt that barriers to prescribing were predominantly patient concerns about tolerability or compliance with blood testing. Almost half of patients surveyed had never heard of clozapine. A narrow majority (57%) of patients said that blood testing would not stop them taking clozapine, with less than half being concerned about side effects. Being admitted to hospital for clozapine initiation was a barrier to treatment for patients. I found that taking clozapine reduces the number of days spent as an inpatient per year. The length of delay to starting clozapine had no effect on the eventual clinical benefit, as measured by inpatient admissions, although younger patients did derive more benefit. The majority of patients in my cohort remained compliant with clozapine for the duration of the study. Those that discontinued were more likely to be male, but no other factors affected the likelihood of stopping clozapine. Patients that discontinued clozapine gained less benefit in clinical outcomes that those that continued taking it. My research shows that clozapine should be introduced as early as possible in the treatment pathway. Not only do younger people benefit more in terms of reductions in time spent in psychiatric institutions, but for all patients clinical and economic savings continue to accrue over time. Strategies that may enable earlier introduction of clozapine should focus on reducing blood testing requirements or making blood testing a less unattractive prospective to patients. Making patients more familiar with clozapine earlier in their illness may help to reduce the fear of side effects, which if they occur must be treated swiftly and robustly. Dedicated and accessible day hospital beds for clozapine initiation may be helpful for some. Every effort should be made to allow patients to remain compliant with clozapine – male patients may especially require support.

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Abbreviations

Abbreviation	Meaning
ICD-10	World Health Organisation International Statistical Classification of Diseases and Related Health Problems
UK	United Kingdom
USA	United States of America
BNF	British National Formulary
EPSEs	Extra-Pyramidal Side Effects
NHS	National Health Service
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
SOHO	Schizophrenia Outpatient Health Outcome
GAF	Global Assessment of Functioning
NICE	National Institute for Health and Care Excellence
CUtLASS	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
SLaM	South London and the Maudsley NHS Foundation Trust
ZTAS	Zaponex Treatment Access System
PRN	Pro Re Nata
POMH	Prescribing Observatory for Mental Health
ANOVA	Analysis of Variance
ANCOVA	Analysis of CoVariance
HSD	Honestly Significant Difference
ONS	Office for National Statistics
MANOVA	Multivariate analysis of variance
LTFU	Lost To Follow Up
BEN	Benign Ethnic Neutropaenia
POCT	Point Of Care Testing
FBC	Full Blood Count
HIV	Human Immunodeficiency Virus
RCT	Randomised Controlled Trial
ECT	Electroconvulsive Therapy

1 Introduction

1.1 Schizophrenia

First described by Kraepelin in 1893 and named by Bleuler in 1908 (1), schizophrenia is a severe and enduring psychotic disorder. It is characterised by symptoms that may include hallucinations, delusions, disorganised speech and behaviour, and a flattened affect (2). The World Health Organisation International Statistical Classification of Diseases and Related Health Problems (ICD-10) (3) describes the main psychopathological phenomena as thought echo, thought insertion or withdrawal, thought broadcasting, delusional perceptions and delusions of control, passivity phenomena, auditory hallucinations, thought disorders and negative symptoms. Affecting about 5 in 1000 people in the UK (4) and with a worldwide incidence of 0.1 – 0.4 per 1000 population (5), it impacts significantly on social and occupational functioning.

Schizophrenia is a costly illness. Whilst the disease itself is not fatal, suffering from it significantly increases mortality (6). Life expectancy may be reduced by almost 15 years (7), not only due to increased risk of suicide or violent death, but also because of the association between serious mental illness and cardiovascular disease, cancer and diabetes. Additionally damaging to quality of life is the associated social dysfunction, which can occur even in the absence of psychotic symptoms. Self-care, occupational functioning, and functioning in personal and community settings are affected (8). The social stigma attached to mental illness is still, despite the efforts of government and charity campaigners, a significant problem (9).

Poorly or incompletely treated schizophrenia imposes costs not just on the individual but also on wider society. Increased bed stay and more frequent and lengthy contact with medical, social, housing and criminal justice services all represent direct costs to the taxpayer. There are also indirect costs which arise when a patient, or carer, is rendered unable or less able to contribute to the workforce. The sum of these excess costs has been estimated at almost

£12 billion per year in the UK (10), and over $62 billion per annum in the USA (11, 12). Clearly, there is much to be gained if schizophrenia can be treated faster and more effectively.

1.2 Pharmacological treatment of schizophrenia

Kraepelin described the deteriorating course of his patient's 'dementia praecox' as being progressive and severe (13, 14), with active symptoms requiring continuous hospitalisation. This is in contrast to other observations of a more relapsing and remitting disease state, where periods of illness may be interspersed with at least partial remission. Modern definitions describe the course of schizophrenia as either continuous, episodic with progressive or stable deficits, or one or more episodes of complete or incomplete remission (3). Further, the diagnosis itself may be defined more precisely as a particular 'type' of schizophrenia; paranoid, hebephrenic, catatonic, undifferentiated, residual, simple or otherwise unspecified (3). Regardless of the label, the mainstay of pharmacological treatment is a group of drugs termed 'antipsychotics'.

The first antipsychotic was discovered serendipitously in 1951, when the antihistamine chlorpromazine was found to have beneficial effects on psychotic symptoms when tested in patients with psychosis (15). The discovery of chlorpromazine led to work that found the key mechanism of action in relief of psychosis to be blockade of dopamine receptors in the brain. As new antipsychotic agents were synthesised, it was recognised that they all appeared not only to improve psychotic symptoms, but also to cause 'neurolepsis' – a slowing of motor response, quiescence and behavioural indifference (16). Despite the frequently severe movement disorders, the arrival of antipsychotic medications on psychiatric hospital wards was transformative. Other drugs, all with a similar pharmacology to chlorpromazine (that is, predominantly dopamine receptor blockade) were produced. This group are commonly referred to as 'conventional', 'typical' or 'first-generation' antipsychotics, of which the British National Formulary (BNF) lists 16 currently available in the UK (17).

In the mid 20th century, psychopharmacologists believed that the antipsychotic benefits and movement disorder side effects of neuroleptic drugs went hand in hand. The prevailing opinion was that without the often physically and socially disabling emergence of movement disorders such as tardive dyskinesias and extra-pyramidal side effects (EPSEs) an antipsychotic would lack therapeutic effect. The synthesis of clozapine in 1959 marked a turning point. Clozapine was the first antipsychotic to demonstrate therapeutic effect in the treatment of psychosis, but with no accompanying EPSEs. Ironically, this fact meant it was largely dismissed as a viable treatment option as clinicians considered the possibility of a drug that could treat schizophrenia but not cause movement disorders literally unbelievable (18). As a result, clozapine was not marketed for schizophrenia treatment until 1972. Clinicians found clozapine to be effective and well tolerated, and its use gathered pace until 1975, when 9 cases of fatal blood dyscrasias secondary to clozapine were reported in Finland (19). Following this, clozapine was withdrawn from the market.

1.3 Treatment-resistant schizophrenia

In the absence of clozapine, it was apparent that for a significant proportion of patients the available 'typical' antipsychotics were either ineffective, or intolerable. These 'treatment-resistant' patients were defined by Kane in 1988 and 1989 (20, 21) as: patients (with a diagnosis of schizophrenia) who had had at least three periods of treatment in the preceding five years with neuroleptic agents (from at least two different chemical classes) at dosages equivalent to or greater than 1000mg/day of chlorpromazine for a period of six weeks, each without symptomatic relief, and no period of good functioning within the preceding five years (20).

Prior to its removal from the market clozapine had started to show promise in clinical settings for the treatment of these patients. Seven trials form the foundation on which evidence for the efficacy and tolerability of clozapine in treatment-resistant schizophrenia has been laid. In 1987, Claghorn and colleagues (22) compared clozapine therapy to chlorpromazine in the treatment of patients who were suffering with tardive dyskinesias or EPSEs induced by

antipsychotic medications. Clozapine was demonstrably superior to chlorpromazine not only in amelioration of EPSEs, but also in magnitude of therapeutic efficacy, and the speed at which this was achieved.

This result was repeated in 1988 (20) and 1989 (21) by Kane et al. For patients with schizophrenia that was unresponsive to at least 3 other antipsychotic trials (and to pre-trial testing with a mean of 61mg/day haloperidol), clozapine provided symptom relief after 6 weeks in 30% of cases, compared with 5% of patients who were given chlorpromazine (20). Honigfeld et al. (23) produced a strikingly similar result in comparison with haloperidol – therapeutic benefit was demonstrated in 31% of the clozapine group, compared with 10% of the haloperidol-receiving patients.

In 1986 Kuha and colleagues (24) published the first review to demonstrate clozapine's long term efficacy. In a retrospective review over 7 years, patients (all of whom had previously failed to adequately respond to other antipsychotics, and had a mean duration of illness of 15 years) experienced symptom improvement in 33% of cases. The longer studies conducted by Povlsen et al. (25) and Lindstrom et al. (26), both retrospective studies over 12 year periods, showed symptom improvement on clozapine in 51% and 40% of patients respectively.

This compelling evidence that clozapine was uniquely effective in treatment-resistant schizophrenia, did not cause movement disorders, and continued to provide symptom relief for many years fuelled enthusiasm for its reinstitution in the psychiatrist's formulary. Close analysis of the individual cases of agranulocytosis and neutropaenia reported in Finland in 1975 suggested that in most cases, the reaction was reversible (on stopping clozapine) and, if detected early and before infection had taken hold, survivable (27). This recognition of clozapine-induced blood dyscrasias being detectable and the risk modifiable, the lack of any comparable successor to clozapine being identified in the intervening years, and, crucially, the work of Kane and colleagues in the late 1980s, led to its re-introduction to the market in 1990.

After clozapine was retrieved from the pharmaceutical sin bin, it was hoped that as well as improving the symptom control of many patients for whom the conventional antipsychotics had failed, it would also lead to the discovery of other antipsychotics that would be effective for the treatment of this neglected group of patients (28). Clozapine has been repeatedly shown to be superior to typical antipsychotics in treatment-resistant schizophrenia (20-26, 29, 30). Following the success of clozapine, other antipsychotics were synthesised (often referred to as 'atypical' or 'second generation' drugs) that aimed to mimic clozapine's effect on psychotic symptoms, and its lack of EPSEs. Risperidone was the first of these newer antipsychotics to the market in 1994, followed by olanzapine in 1996 and quetiapine in 1997 (31). As these atypical antipsychotics were introduced, their potential as haematologically-safer alternatives to clozapine in treatment-resistant schizophrenia was proposed. Randomised trials of risperidone (32, 33) found it to be effective in 33% of treatment-resistant patients. However, switching the risperidone non-responsive patients to clozapine provided symptom relief for a further 56%. Short trials found risperidone to be non-inferior but faster acting (34, 35), but longer trials demonstrated superiority for clozapine (36, 37). Non-inferiority studies of olanzapine in treatment-resistant schizophrenia found it effective (38), but others found clozapine remained superior (39). Studies where clozapine responders were switched to olanzapine were inconclusive – some showing response to olanzapine in 90% of cases (40), others decompensation for 58% of patients (41). It is worth noting that several of these trials were sponsored by the companies marketing the new atypical medication, used low comparator clozapine doses, or included treatment 'intolerant' patients, as well as truly 'treatment-resistant' patients (42). These factors, as well as the now near-impossibility of conducting a truly blinded trial of clozapine as its distinctive side-effect pattern is well known, means that interpretation of the results of any clozapine trial after Kane's rigorous 1988 study should proceed cautiously. This is illustrated by the finding of Samara and colleagues in their network meta-analysis that clozapine is no more effective than any other antipsychotic in treatment-resistant schizophrenia (43). Rather than clinical observations, and the data presented by Kane and others being untrue, it is more likely that

this result reflects the fact that the biases inherent to many clozapine comparator studies are insufficiently controlled (44).

1.4 Schizophrenia treatment guidelines

In the face of what was considered overwhelming evidence for clozapine being the gold standard treatment for neuroleptic-resistant schizophrenia, guidelines in the USA (45-47), UK (48, 49), and internationally (50, 51) were developed. All recommend the use of clozapine after two failed trials of other antipsychotics.

Despite published evidence, and national and international guidelines advising the use of clozapine in treatment-resistant psychosis, prescription rates are almost universally low. It is generally thought that around one third of patients suffering with schizophrenia will have a treatment-resistant illness (52). Given that clozapine is the only recommended treatment for these patients, prescriptions of clozapine within a population with schizophrenia should be around 30% of all antipsychotics. Several large reviews of antipsychotic use in outpatients in the USA have found clozapine to represent just 2% of the total antipsychotic prescriptions (53), with 5.5% of patients with treatment-resistant schizophrenia receiving clozapine (54). Although it is true that clozapine may not be appropriate for all patients, taking into account medical complications precluding treatment, this still presumably leaves more than 90% of patients taking non-clozapine therapies for treatment-resistant schizophrenia that are not evidence-based. Juarez-Reyes and colleagues looked at this in more detail (55), assessing 293 patients in the USA for eligibility for clozapine. They found that 42.9% were eligible, but were not prescribed clozapine.

Similarly low clozapine use has been reported in Israel (2% of all antipsychotic prescriptions) (56), Quebec (6.7% of all antipsychotic prescriptions) (57), South Africa (10% of all antipsychotic prescriptions) (58) Canada (16% of all antipsychotic prescriptions) (59) and Australia (8.4% of prescriptions in treatment-resistant schizophrenia) (60). In Europe, rates vary from very low in Italy (1.3 – 1.5% of all antipsychotic prescriptions) (61) and France (1.2% of all antipsychotic prescriptions) (62), 10.5% in Denmark (63), 17.2% in inpatients in

Germany (64) to 36% in Sweden (65). Prevalence of clozapine appears to be higher in New Zealand (32.8% of all antipsychotic prescriptions) (66), China (40.3%) (67) and Taiwan (26.9%) (67). Data suggest that in most countries, clozapine use has increased in recent years (52), but clearly substantial global variation in prescribing prevalence remains.

Not only is the prevalence of clozapine generally lower than would be expected if guidelines for prescribing were being followed, but for those who are given clozapine the journey to this point seems to have been, for the most part, a long one. Using the commonly accepted Kane criteria (20) as the diagnostic standard for treatment-resistance, the minimum amount of time taken to reach a prescription of clozapine, from first antipsychotic prescription, is probably 12 weeks. This may be shorter if one of the two drugs tried is not tolerated for a full 6 week trial, or longer if the time taken to reach therapeutic dose is taken into consideration. This also assumes that patients are clearly 'treatment-resistant' from the outset of illness – i.e. each of the two antipsychotics trialled fail within the first 6 weeks. An alternative pathway is one of 'developing' treatment-resistance – that is, one or both of the pre-clozapine antipsychotics work for a while, but efficacy 'wears off' as treatment-resistance sets in during the treatment course. Either way, it is clear that using sequential non-clozapine antipsychotics to treat continuing psychotic symptoms after two antipsychotics have failed to do so is almost certain to be ineffective. Kinon et al. (68, 69) found that a third antipsychotic trial conferred less than a 7% chance of response in patients who had already failed to respond to two prior antipsychotics. Similarly, Agid et al.'s trial of 244 patients in their first episode of schizophrenia found that 75% responded to the first flexibly dosed treatment of risperidone or olanzapine. The remaining non-responding 25% were switched to the antipsychotic they didn't try in the first phase, and of these just 17% responded. Following this, non-responders to the second antipsychotic trial were switched to clozapine, with a 75% success rate (70).

Where the time to first prescription of clozapine has been reported, the data vary widely. In their retrospective chart review of 467 outpatients in Canada, Alessi-Severini and colleagues reported the time from first presentation to psychiatric services to first receiving clozapine was an average of 8.9 years for men, and 7.7 years for women (59). In the UK, Taylor et al.

found a delay to receiving clozapine (that is, time from diagnosis of treatment-resistant schizophrenia to clozapine prescription) of 5 years, although the range was wide (0 – 11.1 years) (71). This finding was echoed by Najim et al. ten years later in their study of 42 outpatients taking clozapine in England, who on average took 5 years to reach clozapine after a diagnosis of treatment-resistance, with a range of 0.2 – 16.1 years (72). In New Zealand, Wheeler and colleagues found the time from first presentation to psychiatric services until prescription of clozapine to be 5.3 years (6.5 years in a corresponding UK cohort) (73) - something of an improvement on similar data from just 3 years before this, which described an average of 9.7 years in services before receiving clozapine (66). In the New Zealand group, 37% of patients had started clozapine within the first 5 years of contact with services. In Denmark in 1996, this figure was just 10.4%, and actually reduced to 3.4% by 2003 (63).

Pharmacological strategies employed in treatment-resistant schizophrenia instead of clozapine are frequently ineffective and harmful. Antipsychotics may be prescribed in doses above those that have been licensed ('high dose' prescribing), or in combination with other antipsychotics ('polypharmacy'). Neither of these options is without risk. The compounding of side effects such as sedation, weight gain or other metabolic effects, increased serum prolactin or akathisia is inevitable. Despite these risks, and the availability of a treatment with proven efficacy in refractory schizophrenia, use of non-clozapine treatment strategies in treatment-resistant schizophrenia is widespread. Although it is known to be ineffective (69), prescribing multiple successive non-clozapine antipsychotics rather than the evidence-based two prior to clozapine is common. In Canada, 68% of patients eventually prescribed clozapine received 3 or more antipsychotics first (59). In New Zealand, the average is also 3 antipsychotics pre-clozapine (73), whilst in the UK the mean has been reported as 5.5, with a huge range of 1 – 13 (71). Polypharmacy is also common, with 65% of patients in Taylor et al.'s 2003 study receiving multiple concurrent antipsychotics prior to clozapine (71). In the same area of South East London, Thompson and colleagues found that 13.6% of patients in their study were taking multiple antipsychotics immediately prior to clozapine being prescribed (74).

1.5 Explaining practice

Several demographic descriptors are reported by many authors to be associated with a higher likelihood of being prescribed clozapine. These include being male (54, 75, 76), young (53, 54, 63, 71, 72, 75, 76), white (53, 54, 75) and having a higher illness severity (53, 54, 76). Others, however, have found no effect of gender (63, 66, 67, 77), age (67, 77) or symptom acuity (77). The reason for the demographic influences found by some groups is not immediately apparent. It is probable that patients with non-white backgrounds are more likely to have congenitally lower levels of white blood cells, unrelated to clozapine use, and this may preclude, or at least complicate, starting clozapine. It has been suggested that men have a more severe illness course, and that for younger patients prescribers are more keen to prevent long-term disability, both factors making clozapine prescribing perhaps more likely (54).

Factors relating to the prescribing culture surrounding the clinician and patient also appear to affect clozapine prescribing patterns. Prescribing of clozapine in treatment-resistant schizophrenia seems to remain something of a postcode lottery. In 2000, Purcell and Lewis reviewed the prescribing practices of 12 UK NHS Trusts, and found a 34 fold variation in rates of clozapine prescribing between institutions (78). A repeat study in 2003 (79) showed some improvement, but still a 16 fold variation remained. More recently, Downs and Zinckler compared data from 45 NHS Trusts, finding a persistent 5 fold variation in prescribing (80). Variations in individual clinical practice, including the relative experience of psychiatrists in prescribing clozapine has also been suggested to influence prescription rates by other authors – Nielsen et al. (63) proposed that younger prescribers working in outpatient settings would be less likely to have the required experience and confidence in prescribing clozapine. Wide variations in prescribing within the same country or area (and therefore subject to the same clozapine guidelines and restrictions) but between institutions or individual prescribers would seem to support this view. A review of clozapine prescribing frequency in the USA found that the proportion of clozapine prescribed by individuals, as a percentage of their total prescriptions, ranged from 0 – 89%, and that those who prescribed the highest volumes of

medications were more likely to prescribe clozapine, suggesting that a lack of experience may indeed hinder prescribing (81).

Clinician concerns over what patients are likely to tolerate or comply with are often listed as barriers to clozapine prescribing. Fears that patients will not comply with the compulsory blood testing probably contribute not only to the lower prescription rates in those with comorbid substance abuse disorders (53, 54), but in also patients without these complications (71, 82).

Finally, it is undoubtedly the case that clozapine is a more costly drug to initiate than any other antipsychotic, given the blood monitoring requirements, increased intensity of physical monitoring, additional administrative time and multidisciplinary team activities. Despite this 'front-loading' of costs, clozapine has proven cost-effectiveness when balanced against the reduction in expensive re-admissions. In a study conducted by Essock et al. (83), eligible patients were switched to clozapine from their previous antipsychotic. Those that received clozapine had a 3% readmission rate, those that didn't a 29% rate. Many other groups have also demonstrated the relative cost-effectiveness of clozapine (84-90), even when clozapine was still within patent protection and therefore significantly more expensive than it is now. This message seems to have had an impact on the influence of cost as a barrier to prescribing, with few recent studies citing this is a likely issue, although in some countries this may still be relevant (private medical insurance requirements in the USA may make clozapine unavailable for some (52), and conversely, the minimal cost of clozapine compared to other atypical antipsychotics in China means that it is actually the most commonly prescribed medication for schizophrenia (91)).

1.6 Patient opinions

Even the most effective, evidence-based medications are of no use if the patient does not take them. There can be little doubt that taking clozapine is a particularly arduous process, with attendant pre- and on-therapy regular blood tests, intensive physical health monitoring during initiation, lengthy periods of dose escalation and titration, and an intimidating list of

acute and chronic side effects. It is not surprising that health care professionals may expect patients to at least dislike the idea of clozapine for these reasons, and not unreasonable to fear non-compliance or outright refusal of treatment.

However, despite the obvious inconveniences, patients who are prescribed clozapine are actually found to be adherent to treatment for longer than their counterparts taking non-clozapine antipsychotics (92). When asked directly for their opinions on clozapine, patients who are taking the drug are almost all very positive about their experiences. In a large study of 1126 patients in Australia, of those taking clozapine just 5.3% thought the drug hadn't been helpful (93). Wolfson et al. asked 35 patients who had been taking clozapine for more than 6 months directly about their experience, and found 82% to report benefitting overall from the treatment (94). Where patients experienced side effects, they still preferred clozapine over their previous medications (which were typical antipsychotics – this study was done in 1996), and the majority of patients didn't mind the blood tests either at all, or only a little. This nonchalance about the burden of blood testing was also found by Taylor et al. at few years later; 87% of clozapine patients in this survey felt that the advantages of clozapine outweighed the disadvantage of blood testing (95), with 86% of patients feeling better on clozapine than their previous treatment, and 89% wishing to remain on therapy. This desire to keep taking clozapine was echoed in Waserman and co-worker's interviews of patients prescribed clozapine (96), where improved mood, social and activity levels and a better quality of life meant patients were more satisfied with clozapine treatment than their previous medications, and wanted to continue taking it. The willingness to continue with treatment seems to improve with time – in a study of 80 patients taking clozapine at discharge from inpatient services, Angermeyer et al. found 44% believed they would relapse if they stopped taking the medication when interviewed at discharge, but this increased to 55% six months later (97). In a recent survey of Japanese patients taking clozapine, not only did 66% of those interviewed find clozapine to be effective or extremely effective for them, but 68% also felt it was a safe or extremely safe drug (98).

The obvious bias in all of these studies is of course the selection of patients already successfully established on clozapine treatment, for whom the drug is presumably effective (at least sufficiently to allow participation in research interviews or completion of questionnaires). The views of patients who have experienced therapeutic failure or intolerable side effects with clozapine have not been studied. Similarly uncharacterised in the literature are the opinions of patients who were offered clozapine but did not wish to take it, or those who might be eligible to take it, but have never been given the opportunity to do so.

1.7 Non-prescribing and non-compliance

Despite being apparently well disposed to clozapine when taking it, it is true that not all patients remain adherent with clozapine therapy indefinitely. It is also true that despite an apparent knowledge of the clinical guidelines and benefits of clozapine (discussed below), not all psychiatrists choose to prescribe it in a timely manner. The consequence of a delay in clozapine prescription is not widely studied. In a retrospective review of 402 patients in New Zealand, Harrison et al. found an average patient journey from first presentation to psychiatric services to clozapine prescription of 2.8 years - and the shorter this period was, the fewer subsequent hospitalisations patients experienced (99). This finding was statistically non-significant however, and only included patients who had been taking clozapine for more than 3 years. In their 2015 study of 162 Turkish patients taking clozapine, Ucok and colleagues also found a better response to clozapine if the prescribing delay was shorter (their patient cohort had an average 29 month delay between diagnosis of treatment-resistance and clozapine prescription), the illness duration was shorter, and the patient was younger (100). Most recently, Yoshimura's group in Japan studied 90 patients who had been on clozapine for at least 3 months, and found prescription delay to be a predictor of response to clozapine (101). They describe a 'critical treatment window' (the time from diagnosis of treatment-resistance to clozapine prescription) of 2.8 years, demonstrating a response rate of 82% if patients received clozapine within this window, but 31% if treatment fell outside it.

Once the decision to prescribe clozapine has been made, and the patient has agreed to accept treatment, it is unfortunately the case that not all patients are able to remain adherent with it for as long as their clinical team might wish. Reports of discontinuation rates for clozapine vary, and meaningful comparisons are difficult because outcomes may depend on the study length, degree of support provided to patients, diversity of patient groups (including ethnicity, as this may affect likelihood of discontinuation due to neutropaenia), and definitions of 'discontinuation' (this is usually not clearly described, and where it is varies from 4 day treatment interruptions to 'snapshot' data collection at defined time points). Despite these differences in reporting, most studies found clozapine discontinuation rates to be between 20 and 50%, with the greater proportion of discontinuers doing so in within the first year (56, 60, 77, 90, 102-114). Higher rates of 57% discontinuation were found by Davis et al. in their 15 year retrospective study of 320 patients on clozapine (this group had a strictly defined discontinuation definition of anything over 4 days without clozapine) (102), 55% by Atkinson et al. (106), 53% by Ciaparrelli et al. (107) and 51% by both Vella et al. (60) and Krivoy et al. (56). Lower discontinuation rates were reported by Taylor et al. (18%) (113) and Rascati et al. (16%) (112). Regardless of discontinuation rate, the majority of studies found patients who discontinued treatment were most likely to do so within the first year. Studies that looked at this in more detail found the risk to be front loaded into this year – Davis, Pai, Hayhurst, Kelly, and Rascati and colleagues (90, 102, 108, 112, 115) all found discontinuation of clozapine to be most likely in the first 6 months. Where reported, two main themes of non-adherence (56, 102, 104, 106, 107, 112-115) and side-effects (102, 104, 105, 107, 109, 112, 114, 116, 117) are given as the reasons for discontinuation. Demographic factors that contribute to the likelihood of discontinuation have been found to include older age (56, 102-104) and being African-Caribbean (77, 102, 103, 105, 108, 111, 118), although other authors have also failed to demonstrate these associations (111, 112). It is important to note that patients are in fact more likely to remain compliant with clozapine than with other antipsychotics. The landmark Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trials found 74% of patients discontinued non-clozapine antipsychotics within the first year (119), and in the large Schizophrenia Outpatient Health Outcome (SOHO) trials,

79.5% of patients allocated to clozapine were still taking it at 12 months, a higher concordance rate than for any other antipsychotic medication (120).

Given the evidence for the efficacy of clozapine in most treatment-resistant patients, and the fact that antipsychotic medications are not curative, it would seem obvious that not continuing to comply with treatment would be harmful. Indeed, Atkinson et al. showed that Global Assessment of Functioning (GAF) scores were lower after stopping clozapine (106), and Hayhurst and colleagues (90) found that clozapine discontinuers had more, and longer hospital admissions. Interestingly, some groups report that non-improvement in symptoms was a reason for discontinuing clozapine (112, 114, 116), and this seems not only unfortunately predictable (clozapine is not effective in all patients) but also clinically challenging, since the ineffectiveness of any other medication is also predictable in this circumstance. The scrabble for symptom control after stopping clozapine is reflected in Atkinson et al.'s finding that 74% of patients had two or more antipsychotics prescribed in the year after discontinuation, with 44% of patients receiving polypharmacy (106).

1.8 Improving practice

Audit and feedback of adherence to guidelines go some way to improving practice (increasing clozapine prescribing from a 21% baseline rate to 35% following audit in one study (75)), but underuse of clozapine remains commonplace. The UK's National Institute for Health and Care Excellence (NICE) states that in 2002, just 21% of patients diagnosed with treatment-resistant schizophrenia were receiving clozapine (121). By 2010, this figure had increased to 54% (122), leaving 46% of patients without the one treatment proven to work in their condition. An audit by the Royal College of Psychiatrists in 2012 echoed this statistic, finding that 43% of treatment-resistant patients had not been offered clozapine (123), and that stark differences in prescribing practices between clinicians remained.

Several authors have suggested that a lack of knowledge is the principal barrier to prescribing in line with evidence-based recommendations (124). In 1994 Kissling presented a cohort of psychiatrists with clinical scenarios and asked them to make treatment

recommendations (125). Vastly different answers were received, many of them outside prescribing guidelines of the time. A lack of prescriber knowledge of recommendations was blamed. Patel et al. (126) extended this theory to depot medication, showing that a poor knowledge of aspects of medication prescribing results in poor attitudes to the drug, and lower levels of prescribing.

More recent surveys have shown that knowledge of guidelines seems to be improving, with 88% of psychiatrists recognising that clozapine should be commenced after two failed trials of other antipsychotics (127). Despite this, within the same cohort of prescribers a clear reluctance to prescribe clozapine remained; 99% of doctors said they would use clozapine for treatment-resistant schizophrenia, and yet 64% would rather co-prescribe two other antipsychotics instead of starting clozapine. Guidelines are clearly only responsible for one part of the prescribing decision. Personal experiences, local context, prescribing cultures, and patient characteristics are all involved (128). Lloyd et al. (129) analysed attitudes to prescribing within the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) in 2005, and found guidelines to constitute only 8% of the prescribing decision, compared with review articles or randomised controlled trials (35%), or clinician experience (17%).

There are few studies of guideline adherence, and where studied it is shown to be poor (130, 131). This also seems to be influenced by the demographics of the patient - Weinmann et al. (132) demonstrated that patients with chronic illness are at higher risk of not receiving care in line with guidelines. This is borne out specifically in relation to clozapine prescribing; Wheeler et al. (75) found that older patients were less likely to be prescribed clozapine, and Taylor and colleagues (71) showed that the delay to starting clozapine was increased for those over the age of 30. It also appears to hold true for speaking to patients about medication; Hamann et al. (133) showed that psychoeducation tended to be reserved for younger patients with a shorter duration of illness and fewer inpatient admissions. This is despite evidence that talking to patients about their treatment plans improves outcomes (134).

A lack of communication between prescriber and patient may in part explain the repeated findings that the views of patients of clozapine differ markedly from what prescribers think their views are. A study by Hodge et al. (135) found that 81% of patients considered the side effect profile of clozapine to be better than that of the antipsychotics they had been taking previously. Just 17% of their clinicians thought this to be the case. 48% of prescribers thought that patients wouldn't mind about having their blood monitored whilst on therapy – in fact, 81% of patients said they didn't mind. Few clinicians (30%) thought clozapine would be a patient's favourite drug. When asked, 85% of patients preferred clozapine over any other antipsychotic. Day and colleagues also demonstrated this mismatch of opinions in their survey of patients with schizophrenia and psychiatrists (136). They found clinicians frequently overestimated the magnitude of distress associated with a variety of side effects compared with that reported by the patients, showing an apparent lack of understanding by psychiatrists of the adverse effects their patients are worried about.

For patients at South London and the Maudsley NHS Foundation Trust (SLaM), treatment delay to clozapine in 2001 was an average of 5 years (71). The authors at the time hypothesised several possible reasons for this; patient reluctance to comply with blood tests, clinician fears over probable non-compliance with medication or the development of agranulocytosis or other side effects, cost, lack of experience in prescribing clozapine, and lack of clinician confidence in the clinical effectiveness of clozapine in treatment-resistant schizophrenia. These theories were not tested at the time. As yet, no research group has clarified the barriers to prescribing clozapine as perceived by clinicians working directly with patients with schizophrenia, with a view to generating potential solutions.

1.9 Aims

The aim of this thesis is to first examine whether there remains a delay to clozapine prescribing for patients at SLaM. A retrospective review of clinical data looks at prescribing strategies before clozapine initiation and the length of time between diagnosis of treatment-resistance and clozapine prescription. Secondly, I report a questionnaire study that probes

the attitudes and experience of clinicians working within the same Trust towards clozapine. This aims to reveal barriers to clozapine prescribing, and put forward solutions for improving access to the drug. Following this, I describe the results from interviews conducted with patients eligible for, but not taking clozapine in order to study the extent to which the opinions of medical teams tally with those of their patients regarding clozapine initiation. Retrospective clinical data collection is used to conduct a mirror-image study to observe the effect of any delay to clozapine prescribing on patient outcomes. Finally, the data are interrogated for detailed information about those patients that discontinue clozapine, appraising the effect of stopping clozapine on clinical outcomes, and elucidating predictors for clozapine discontinuation.

1.10 Ethics

All studies described in this thesis were approved by the Trust Drug and Therapeutics Committee. Research Ethics Committee approval was not required for the studies described in chapters 2, 5 and 6 as the research was considered a clinical audit, designed to answer whether the service reaches predetermined prescribing standards. They involved analysis of existing data and no allocation of treatment or randomisation was carried out. Research Ethics Committee approval was not required for the study described in chapter 3 as the research involved NHS and social care staff recruited as research participants by virtue of their professional roles. The survey of patient attitudes to clozapine outlined in chapter 4 did not require Research Ethics Committee approval as this study was considered a service evaluation or quality improvement project, conducted to define clinical care and answer 'what standard does this service achieve'. It did not involve allocation of treatment or randomisation.

2 Is there a delay to clozapine use?

2.1 Introduction

In about one in three patients with schizophrenia, the condition is treatment-resistant (122, 137, 138). This has been defined as an inadequate response to sequential treatment with two different antipsychotics at adequate dose, duration and adherence (48, 138). Clozapine is the only drug treatment currently licensed for patients with treatment-resistant schizophrenia, and is associated with lower rehospitalisation rates compared with other antipsychotics (138, 139). However, long delays in initiating clozapine in routine clinical practice have been reported (66, 71, 99, 108). In 2001, research showed that patients at SLaM experienced a mean delay of 5 years to receive clozapine (71). Since this study, clinical guidelines from NICE and other organisations have been published recommending that clozapine be offered at the earliest opportunity for treatment-resistant patients (49, 140). Whilst there is little clear benefit over other antipsychotics of clozapine as a first-line treatment (141) a study of patients presenting to services for the first time found that 75% of patients who failed to respond to sequential 4 week treatment trials with two different antipsychotics then responded to clozapine (142).

Guidelines issued by NICE and other organisations also state that there is little evidence to support the use of antipsychotic doses above the licensed maximum dose or for antipsychotic polypharmacy (other than for short periods during cross-tapering) and recommend that these strategies should be used only in exceptional cases (49, 140). The aim of this study is to determine if prescribing practice at SLaM followed NICE clinical guidelines. Specifically, I sought to determine the time taken to initiate clozapine after a patient had completed adequate treatment with two different antipsychotic drugs, and the frequency of antipsychotic polypharmacy and high dose antipsychotic treatment prior to clozapine initiation.

2.1.1 Objectives

- To describe the pre-clozapine antipsychotic prescribing histories of a cohort of patients who received clozapine.
- To calculate the theoretical delay to clozapine use for these patients.
- To establish whether the duration of the psychotic illness, the age of the patients, their ethnicity, gender or diagnosis affects the theoretical delay to clozapine prescribing.

2.2 Method

A list of all patients who commenced clozapine under the care of SLaM between 1st January 2006 and 15th April 2010 was obtained from the Zaponex Treatment Access System (ZTAS) patient monitoring database. The list was inclusive of outpatients, inpatients, and those being treated by tertiary referral services. The clinical records of these patients were interrogated for the following demographic data:

- Gender
- Age (defined as the date of birth to the end date of the study)
- Primary diagnosis (ICD-10 criteria)
- Self-reported ethnicity (categorised as White British/other, Black British/other, Asian British/other, or mixed)

Clinical data were extracted by hand-searching of the clinical notes. The following were recorded:

- Duration of illness (defined as the time from the first recording of the diagnosis of a psychotic illness by a clinician to the end date of the study)
- Antipsychotic treatment history

Antipsychotic treatment episodes were recorded and categorised in the following way:

- Adequate treatment episode:
    - Atypical drug

    - Typical drug
    - Depot drug
- Inadequate treatment episode:
    - Due to duration <6 weeks
    - Due to non-therapeutic dose
    - Due to duration <6 weeks and non-therapeutic dose

Therapeutic doses of oral antipsychotics were determined in accordance with the Maudsley Prescribing Guidelines (138). Minimum therapeutic doses of depot medications were as defined by Taylor in his 2009 paper (143). Where minimum doses were not available from these sources, expert pharmacists were consulted and a consensus reached. The following table sets out the doses used to define adequate treatment doses during data collection.

Table 2-1 Minimum effective doses of antipsychotics

Antipsychotic	First episode (mg)	Subsequent episodes (mg)
Typical antipsychotics		
Chlorpromazine	200	300
Haloperidol	2	>4
Sulpiride	400	800
Trifluoperazine	10	15
Atypical antipsychotics		
Amisulpride	400	800
Aripiprazole	10	10
Asenapine	10	10
Iloperidone	4	8
Olanzapine	5	10
Quetiapine	150	300
Risperidone	2	3
Sertindole	12	12
Ziprasidone	80	80
Depot antipsychotics		
Flupenthixol decanoate	60 every 2 weeks	60 every 2 weeks
Fluphenazine decanoate	50 every 2 weeks	50 every 2 weeks
Haloperidol decanoate	100 every 2 weeks	100 every 2 weeks
Perphenazine decanoate	150 every 2 weeks	150 every 2 weeks
Pipothaizine palmitate	50 every 2 weeks	50 every 2 weeks
Zuclopenthixol decanoate	300 every 2 weeks	300 every 2 weeks
Olanzapine palmoate	300 every 2 weeks	300 every 2 weeks
Risperidone microspheres	37.5 every 2 weeks	37.5 every 2 weeks

Pro Re Nata (PRN, 'as required') antipsychotic doses were not recorded as treatment episodes. Continuous administration of an antipsychotic for at least 24 hours was required for consideration as a separate treatment episode. Where adherence to medication was

clearly documented as poor or non-existent, the episode was designated ‘inadequate’.

Multiple treatment episodes of the same drug were counted as different episodes if they were separated by at least 6 weeks. Polypharmacy was recorded if two antipsychotics were prescribed concurrently, both at adequate doses, for more than 6 weeks. Supra-maximal doses of antipsychotics were recorded and defined by the licensed maximum doses for drugs published in the BNF 61st edition (144). Where polypharmacy occurred, the total combined dose was calculated and determined as above or within BNF limits as outlined in the Prescribing Observatory for Mental Health (POMH) audit guidelines (145).

Data were then extracted as follows:

- Total number of antipsychotic treatment episodes prior to the first use of clozapine
- Number of different antipsychotic drugs used before the first use of clozapine
- Number of adequate antipsychotic treatment episodes before first clozapine use
- Number of adequate treatment episodes of different antipsychotics before first clozapine use
- Number of antipsychotic treatment episodes with different atypical drugs before first starting clozapine

The primary outcome measure was the maximum theoretical delay in clozapine initiation. This was defined as: the date of the end of the second adequate treatment episode (6 weeks at an adequate dose) to the date of the first prescription of clozapine. The period before January 1990 was excluded as clozapine was not then available in the UK. Where data were missing either for duration of treatment episodes or doses of drugs, the episode was excluded from analyses of adequate trials, but counted for the purposes of the total number of antipsychotic treatment episodes. Every effort was made to gather complete prescribing histories for all patients, but where this was not possible, demographic data were gathered and these patients designated ‘excluded’.

2.2.1 Statistical analysis

Data were analysed using Microsoft Excel 2010 and IBM SPSS Statistics 21. Bias was tested using *z*-scores. Possible sources of bias in the data are outlying data scores, and violations of assumptions (normality and homoscedasticity or homogeneity of variance). Outliers can bias both parameter estimates and the errors associated with those estimates, and so should be identified if present. *z*-scores can be used to find outliers, as they express the data in terms of a distribution with a mean of 0 and a standard deviation of 1. In a normal distribution, approximately 5% of the *z*-scores would be expected to be greater than 1.96, 1% to have values greater than 2.58, and none to be greater than 3.29 (146). Where required, *z*-score testing was followed up with normality testing, using the Kolomogorov-Smirnov and Shapiro-Wilk tests to compare the z-scores of the data sample to a normally distributed set of scores with the same mean and standard deviations. If the tests are non-significant ($p > 0.05$), the distribution of the sample is considered to be normal.

The variance of the data affects the estimation of the parameters in the model when using the method of least squares, and also the null hypothesis significance testing (test statistics assume the variance to be equal across different values of the predictor variable). For accuracy of these results, it is therefore important to assume homoscedasticity, or homogeneity of variance. Levene's test was used to test the null hypothesis that the variances in different groups are equal. If Levene's test is significant ($p < 0.05$), the null hypothesis is incorrect and the variances are significantly different – that is, the assumption of homogeneity of variances has been violated.

In order to reduce the impact of this bias to the data, four methods can be employed; trimming the data, winsorising, bootstrapping, or transforming. Trimming the data (deleting the patients who contribute outlying scores) is not appropriate, since the sample is entirely drawn from the target population. Winsorising (changing outlying data scores to the next highest score that is not an outlier) is also inappropriate for the same reason. Bootstrapping the data is considered the most robust way of dealing with bias in this sort of data set, as it applies

tests that are unaffected by outliers, and does not rely on the assumption of normally distributed data. This is the technique that will be used for the following statistical tests.

In order to assess differences between included and excluded patients, an independent samples *t*-test was used. Each patient was either included or excluded and could not be a member of both groups at different times, so a paired-samples *t*-test was not appropriate. The *t*-test is carried out by comparing the sample means for each set of data (in this case, included versus excluded patients). If the samples come from the same population, the means are expected to be roughly equal. As the *t*-test uses numerical sample means, it can only be applied to continuous variables (in this data set, age and the duration of illness).

To test for differences between included and excluded patients in terms of the categorical variables, chi-square tests were carried out. Pearson's chi-square test compares the frequencies observed in certain categories compared to those expected to occur in those categories by chance. For this data set, the test analyses how many patients from each group (included or excluded) fall into each category (for gender, the categories are male or female; for ethnicity the categories are white, mixed race, Asian – and so on) – this is the frequency. For variables with two categories (i.e. gender; the categories are male or female), the expected frequency of values in each category must be more than 5. For variables with 3 or more categories (i.e. ethnicity and diagnosis), the expected frequency of values in each category must be greater than 1, and no more than 20% of the expected counts should be less than 5. If these assumptions are not met, the power of the test statistic is drastically reduced.

2.3 Results

Table 2-2 Patient demographics

		Total sample, n = 224	**Included patients, n = 149**	**Excluded patients, n = 75**	***p***
Age (years), mean (range)		37 (15 – 75)	34 (15 – 75)	43 (22 – 75)	<0.0001
Gender	Male, n (%)	142 (63.4)	102 (68.5)	40 (53.3)	0.027
	Female, n (%)	82 (36.6)	47 (31.5)	35 (46.70)	
Ethnicity	White, n (%)	106 (47.3)	61 (40.9)	45 (60.0)	0.026
	Black, n (%)	81 (36.2)	61 (40.9)	20 (26.7)	
	Asian, n (%)	12 (5.4)	7 (4.7)	5 (6.7)	
	Mixed, n (%)	14 (6.3)	12 (8.1)	2 (2.7)	
	Other, n (%)	11 (4.9)	8 (5.4)	3 (4.0)	
Diagnosis	Schizophrenia, n (%)	165 (73.7)	116 (77.9)	49 (65.3)	0.012
	Schizoaffective disorder, n (%)	36 (16.1)	24 (16.1)	12 (16.0)	
	Bipolar disorder, n (%)	17 (7.6)	8 (5.4)	9 (12.0)	
	Other, n (%)	6 (2.7)	1 (0.7)	5 (6.7)	
Duration of illness (years), mean (range)		11 (1 – 45)	9 (1 – 30)	16 (1 – 45)	<0.0001

2.3.1 Bias

Assessment of bias in the data set shows that the sample includes outlying data that may influence the results, and also that the sample values may not be normally distributed, and homogeneity of variance cannot be assumed for all variables.

The frequency of *z*-scores in this data set are shown in Appendix A (Table 7-1). For this data set, 2% of the cases were above 3.29 (extreme cases), 2.7% were greater than 2.58 (more than the expected 1% for probable outliers), and 7.4% had values greater than 1.96 (potential outliers). The remaining cases constitute 92.6% of the values, and these lie within the normal range. Therefore the data are not consistent with what would be expected from a normal distribution, where 95% of the data would be expected to fall with the normal range.

It is important to establish the normality of the data set, as significance tests relating to the parameters of the data model depend on normality of the distribution. The central limit theorem, which is generally accepted to apply to sample sizes over 30 (as presented here), means that normality can usually be assumed for large data sets (where outliers have more of an influence). As the z-scores showed a problem with outlying data scores in this sample,

I performed tests for normality. The results from these tests are presented for included and excluded patients in Appendix A (Table 7-2). The tests for age, sex, ethnicity, primary diagnosis, duration of illness and theoretical delay for included patients were all highly significant, D(149), $p < 0.0005$. This indicates that these distributions are not normal. The tests for age, sex, ethnicity and primary diagnosis for excluded patients were also highly significant, D(75), $p < 0.05$, again indicating a non-normal distribution.

The results for Levene's test are presented in Appendix A (Table 7-3). The test can be based on differences between scores and the mean or the median (both are shown in the table). The latter is preferable as it is less affected by outlying data, which the z-scores discussed earlier demonstrate are present in this data set. For the variable of age, the variances were equal for included and excluded patients, F(1, 217), $p = 0.074$, showing no significant difference for patients in each group based on this variable. For gender, the variances were unequal for included and excluded patients, F(1, 217), $p = 0.025$, indicating a significant difference between included and excluded patients within this variable. For ethnicity, the variances were equal for included and excluded patients, F(1, 217), $p = 0.105$, showing no significant difference for patients in each group based on this variable. For diagnosis, variances were unequal for included and excluded patients, F(1, 217), $p = 0.005$. For duration of illness, variances were unequal for included and excluded patients, F(1,217), $p < 0.0005$, indicating a significant difference between included and excluded patients within both these final variables.

2.3.2 Comparison of included and excluded patients

The characteristics of the patients who were included were compared to those who were excluded from data analysis, to ensure no differences in demographics were present that would indicate a bias in the selection of the patient population. In order to assess differences between these two groups of patients, an independent samples *t*-test was used. Excluded patients tended to be older, and this difference, -8.8, BCa 95% CI [-12.2, -5.4] was significant t(217) = -5.4, $p = <0.0005$). Excluded patients also tended to have a longer duration of illness, and this difference, -7.8 BCa 95% CI [-10.0, -5.8] was significant t(217) = -6.6, *p*

<0.0005. Based on the odds ratio, the likelihood of being included in the analysis was 1.9 times higher if the patient was male than if the patient was female. The excluded patient group was made up of a higher proportion of white patients and a lower proportion of black patients than the included group. Patients were 3.71 times more likely to be excluded from the analysis if they had a diagnosis other than schizophrenia or schizoaffective disorder. The results of the independent samples *t*-test for the continuous variables, along with the corresponding bootstrapping test results (as discussed above) are presented in Appendix A (Table 7-4 and Table 7-5) and described in more detail below.

The data from Levene's test, carried out previously but repeated here as part of the *t*-test, show that the assumption of homogeneity of variance for both variables has been violated (Levene's test is significant at $p = 0.042$ for age, and $p < 0.0005$ for duration of illness). Equal variances should therefore not be assumed. The two-tailed value of p is < 0.0005 for both variables, and so I conclude that there is a significant difference between the means of the two groups for both age and illness duration. The bootstrapping procedure re-estimates the standard error of the mean difference, and shows the difference between the group mean ages as -8.8, with a confidence interval of -12.2 to -5.4. This confidence interval implies that the difference between the means in the population is negative (the interval range is negative) and cannot be zero (the interval range does not cross zero). The bootstrap procedure therefore confirms that there is a significant difference in mean age between the two groups of patients. The same applies to the duration of illness variable, where bootstrapping shows the difference between the group mean illness durations as -7.8, with a confidence interval of -10.0 to -5.8.

The results of the chi-square test for the differences in gender distribution across the included and excluded patient groups are presented in Appendix A (Table 7-6). The test shows that no combination of categories contained less than 5 expected counts, and so this assumption is met and no further data manipulation is required. The chi-square test demonstrates that there is a significant association between gender and whether or not a patient was included in the analysis χ^2 (1) = 4.917, $p = 0.027$. The odds of male patients being included in the

study can be calculated by dividing the number of male patients that were included in the analysis (102) by the number of male patients that were excluded from the analysis (40) = 2.55. The same odds can be calculated for female patients, by dividing the number of female patients that were included in the analysis (47) by the number of female patients that were excluded from the analysis (35) = 1.34. The odds ratio is the odds of male patients being included in the study (2.55) divided by the odds of female patients being included in the study (1.34) = 1.90.

The results of the chi-square test for the differences in ethnicity distribution across the included and excluded patient groups are presented in Appendix A (Table 7-7). The test shows that 5 combinations of categories contained less than 5 expected counts. As this variable consists of more than two categories (white, mixed race, Asian and Asian British, Black or Black British, other, not stated) it is not possible to use Fisher's exact test to correct this violation. Instead, it is necessary to either collect more data (which is not possible), accept the loss of statistical power (which is not desirable), or collapse the categories within the variable (i.e. merge some categories together). The detailed breakdown of the expected counts for each category within the variable are shown in the crosstabulation table in Appendix A (Table 7-8). This table shows that the expected counts are less than 5 for the categories of mixed race, Asian or Asian British, other, and 'not stated'. By combining these categories together into one larger 'other' category, this allows the expected frequencies in all categories to be more than 5 (data shown in the second crosstabulation table presented in Appendix A, Table 7-9). The new categories within the ethnicity variable are therefore white, black, and 'other'.

The results of the chi-square test for the differences in ethnicity distribution across the included and excluded patient groups, with the new categories within this variable are presented in Appendix A (Table 7-10). The test demonstrates that there is a significant association between ethnicity and whether or not a patient was included in the analysis, χ^2 (2) = 7.333, p = 0.026. The odds of white patients being included in the study can be calculated by dividing the number of white patients that were included in the study (61) by

the number that were excluded (45) = 1.36. The same odds can be calculated for black patients; 61/20 = 3.05, and for those in the other ethnic groups; 27/10 = 2.7. The crosstabulation table shows that of all the patients that were excluded, 60% were white. Of the patients that were included, 40.9% were white. These proportions are significantly different (at $p > 0.05$), as denoted by different subscript letters in the table. The proportions of black patients in each group also differ significantly, with 26.7% of excluded patients and 40.9% of included patients being black. For those in the 'other ethnicity' category, 13.3% were excluded, and 18.1% were included.

The results of the chi-square test for the differences in primary diagnosis distribution across the included and excluded patient groups are also presented in Appendix A (Table 7-11). As for ethnicity, the test shows that assumptions have been violated with 2 combinations of categories containing less than 5 expected counts. The detailed breakdown for the expected counts for each category within the variable are shown in the crosstabulation table in Appendix A (Table 7-12). The table shows the expected counts for schizophrenia and schizoaffective disorder to be above 5, but those for the 'other' diagnosis category to fall below this minimum level. The expected counts for bipolar disorder are lower than those for the other diagnoses, but within the required parameters. Combining the 'other' and bipolar disorder categories is a sensible approach, and this new crosstablulation table is also presented in Appendix A (Table 7-13). The new categories for the diagnosis variable are now schizophrenia, schizoaffective disorder, and 'other'. Treating the data in this way allows all expected counts to be above 5.

The results of the chi-square test for the differences in diagnosis distribution across the included and excluded patient groups, with the new categories within this variable are presented in Appendix A (Table 7-14). The test demonstrates that there is a significant association between diagnosis and whether or not a patient was included in the analysis χ^2 (2) = 8.808, $p = 0.012$. The crosstabulation table shows that the proportions of patients in each group differed significantly for schizophrenia and 'other' diagnoses (indicated by different subscript letters). The proportions of patients with schizoaffective disorder did not

differ significantly across the included and excluded groups. The odds of a patients being excluded from the study if their diagnosis was schizophrenia can be calculated by dividing the number that had a diagnosis of schizophrenia and were excluded (49) by the number with this diagnosis that were included (116) = 0.42. The odds of a patient being excluded from the study if their diagnosis was 'other' can be calculated by dividing the number that had an 'other' diagnosis and were excluded (14) by number that had an 'other' diagnosis but were included (9) = 1.56. The odds ratio for exclusion from the study can be calculated by dividing the odds of being excluded if the diagnosis was 'other' (1.56) by the odds of being excluded if the diagnosis was schizophrenia (0.42) = 3.71.

2.3.3 Treatment episodes

The characteristics of the pre-clozapine antipsychotic trials as gathered by interrogation of the clinical notes are given in the table below (Table 2-3). The total number of antipsychotic prescriptions prior to clozapine commencing ranged from 1 to 20, with a mean of 5.62. This included all prescriptions prescribed regularly for more than 24 hours (i.e. excluding the use of PRN antipsychotics). Of these antipsychotic trials, some were repeated prescriptions (at different time points but for the same patient) of the same antipsychotic. Excluding these episodes of a subsequent use of a previously prescribed antipsychotic, the number of different antipsychotics used in the population prior to clozapine was a mean of 3.89, with a range of 1 to 10. Excluding inadequate trials of antipsychotics, the total number of different antipsychotics prescribed before clozapine (at therapeutic doses and for at least 6 weeks) ranged from 0 to 8, with a mean of 2.81. There was a mean of 0.63 episodes per patient of polypharmacy (range 0 – 6), defined as the prescription of two or more antipsychotics for more than 6 weeks concurrently. The number of depot antipsychotics prescribed in the pre-clozapine period ranged from 0 – 8, with a mean of 1.28 per patient. The total number of atypical antipsychotics prescribed ranged from 0 to 5, with a mean of 2.51. When only adequate trials (in terms of dose and duration) were considered, the range reduced to 0 to 4, and the mean to 1.97.

Table 2-3 Treatment episodes

	Minimum	Maximum	Mean	Std. Deviation
Total number of 'regular' antipsychotic prescriptions before clozapine, at any dose for >24h	1	20	5.62	3.521
Number of different antipsychotics used prior to clozapine	1	10	3.89	1.860
Number of documented episodes of adequate trial (>6 weeks)	0	12	3.72	2.351
Number of different antipsychotics given adequate trial	0	8	2.81	1.486
Polypharmacy (two or more antipsychotics >6 weeks)	0	6	0.63	1.074
Number of atypicals given adequate trial	0	4	1.97	0.930
Total number of atypicals used (adequate AND inadequate trials)	0	5	2.51	1.037
Number of episodes of depot antipsychotic use	0	8	1.28	1.607

Details of the reasons for classification of the antipsychotic trials as inadequate are given in the table below (Table 2-4). In total, patients received a mean of 1.88 inadequate trials of medication prior to clozapine initiation, with a range of 0 – 10. Of these inadequate trials, a mean of 0.56 were due to dosing below that considered therapeutic (range 0 – 6). A mean of 0.59 trials were inadequate due to a duration of less than 6 weeks (range 0 – 5). A combination of both of these factors accounted for the inadequacy of a mean of 0.12 trials (range 0 – 3), and for a mean of 0.61 of the trials (range 0 – 7) the information available in the clinical notes was not available to classify further.

Table 2-4 Inadequate treatment episodes

	Minimum	Maximum	Mean	Std. Deviation
Inadequate dose	0	6	0.56	0.982
Inadequate duration	0	5	0.59	0.908
Inadequate dose and duration	0	3	0.12	0.434
Unavailable information	0	7	0.61	1.044
Total	0	10	1.88	2.043

2.3.4 Regression analysis

In order to establish whether any of the variables associated with the data (duration of illness, age, ethnicity, gender or diagnosis) affect the theoretical delay to clozapine initiation, regression analysis was used. For the continuous variables of age and illness duration, simple linear regression was employed. As age and illness duration may also be expected to influence each other (increased age at the time of clozapine initiation would be likely to be

associated with an increased duration of illness up to this point), multiple regression analysis was then used to establish any confounding relationship between these variables and the effect on the theoretical delay to clozapine use.

For the purpose of this analysis, age was defined as the time from the date of birth to the point at which the criteria for diagnosis of refractory illness were met, and duration of illness as the time from the onset of psychosis to the point at which the criteria for diagnosis of refractory illness were met. This avoids including the clozapine delay time period in these time spans; without doing so, the theoretical delay and age or duration of illness would be inherently related to each other and any independent relationship would be masked. This problem is known as 'part-whole correlation', where one variable is derived from the other and an inherent correlation may exist between the two (147). For both variables, where a diagnosis of refractory illness was not met, this date was taken as the date at which clozapine was commenced.

The effect of the categorical variables of gender, ethnicity and diagnosis on the theoretical clozapine delay was examined using one-way analysis of variance (ANOVA) (where there were more than two categories within the variable – as for ethnicity and diagnosis) or independent *t*-test (where there were only 2 categories, as for gender).

2.3.4.1 Illness duration

The scatterplot showing the relationship between the theoretical delay to clozapine initiation and the duration of the illness is presented in Appendix A (Figure 7-1). The pattern of the data shows that a negative relationship exists between the variables, whereby the longer the duration of the illness, the shorter the theoretical delay to clozapine use. The equation of the regression line, annotated on the scatterplot as y = 45.02 + -0.05 x, means that the theoretical delay to clozapine use (in months) can be calculated by: 45.02 + -0.05 times the duration of the illness (in months).

The summary of the regression model is shown in Appendix A (Table 7-15 Regression model summary). The table shows that $R = 0.037$, and because there is only one predictor (duration

of illness), this value is representative of the correlation between theoretical delay to clozapine initiation and the duration of the psychotic illness. The value of $R^2 = 0.001$; the R^2 represents the amount of variance in the outcome explained by the model, in terms of a proportion. Therefore the duration of illness can account for 0.1% of the variation in the theoretical delay. This means that 99.9% of the variation in the theoretical delay to clozapine use cannot be explained by the duration of illness alone, and there must be other variables that are influencing the outcome.

Next, I conducted an ANOVA, in order to establish whether the regression model presented above results in a significantly better prediction of the theoretical delay to clozapine use than if the mean theoretical delay was used alone. The results of this are presented in Appendix A (Table 7-16 ANOVA). The table provides the sum of squares with associated degrees of freedom (df), and the average sum of squares (noted in the table as mean square, calculated by dividing the sum of squares by the associated degrees of freedom). The *F*-ratio is calculated by dividing the value of the mean squares for the model by the residual mean squares, and for these data *F* is 0.206, which is non-significant at a *p* value of 0.651. Therefore the regression model does not predict theoretical delay significantly well (no better than using the mean value of the theoretical delay alone).

The model parameters (coefficients) give an indication of the individual contribution of variables in the model, and are presented in Appendix A (Table 7-17 Model coefficients). The value b_0 is the *Y* intercept of the scatterplot discussed earlier. The table shows that b_0 (the constant) is 45.051, therefore when theoretical delay is zero (the intercept of the *X* axis on the scatterplot), the expected duration of illness is 45.051 months. The data table also shows the value of b_1 (the gradient of the regression line) as -0.048. This value represents the change in the outcome associated with a unit change in the predictor, therefore for each extra month of illness, the theoretical delay to clozapine is decreased by 0.048 months. The value of the regression coefficient (*b*) should be different from zero if the duration of illness has a significant impact on the ability of the model to predict the theoretical delay to clozapine use. This is tested using *t*-test, the results of which (and associated *p* values) are given in

the final two columns of the table. The result of the *t*-test for the duration of illness is non-significant at a *p* value of 0.651, meaning that the regression coefficient (*b*) for this variable is not significantly different from zero. Therefore in the case of the duration of illness, this makes no significant contribution ($p = 0.651$) to predicting the length of delay to clozapine initiation.

As explained previously, these data may not conform to normality assumptions and so I carried out bootstrapping procedures for the model parameters. The results from this are given in Appendix A (Table 7-18). The bootstrap confidence intervals indicate that the population value for *b* (the value of the regression coefficient) for the duration of illness is likely to fall between -0.227 and 0.243. As this interval includes zero, there is no relationship between theoretical delay and duration of illness in the population. Additionally, the significance associated with this confidence interval is $p = 0.635$, which is non-significant.

2.3.4.2 Age

The scatterplot showing the relationship between the theoretical delay to clozapine initiation and age is presented in Appendix A (Figure 7-2). The pattern of the data shows that a negative relationship exists between the variables, whereby the older the age of the patient, the shorter the theoretical delay to clozapine use. The equation of the regression line, annotated on the scatterplot as y = 66.06 + -0.07 x, means that the theoretical delay to clozapine use (in months) can be calculated by: 66.06 + -0.07 times the age of the patient (in months).

The summary of the regression model is shown in Appendix A (Table 7-19). The table shows that $R = 0.147$, and because there is only one predictor (age), this value is representative of the correlation between theoretical delay to clozapine initiation and the age of the patient. The value of $R^2 = 0.022$, therefore the age of the patient can account for 2.2% of the variation in the theoretical delay. This means that 97.8% of the variation in the theoretical delay to clozapine use cannot be explained by age of the patient alone, and there must be other variables that are influencing the outcome.

Next, I conducted an ANOVA, in order to establish whether the regression model presented above results in a significantly better prediction of the theoretical delay to clozapine use than if the mean theoretical delay was used alone. The results of this are presented in Appendix A (Table 7-20). The *F*-ratio = 3.238, which is not significant at a *p* value of 0.074. Therefore the regression model does not predict theoretical delay significantly well (no better than using the mean value of the theoretical delay alone).

The model parameters (coefficients) give an indication of the individual contribution of variables in the model, and are presented in Appendix A (Table 7-21). The value b_0 is the *Y* intercept of the scatterplot discussed earlier. The table shows that b_0 (the constant) is 66.055, therefore when theoretical delay is zero (the intercept of the x axis on the scatterplot), the expected age of the patient at the time of starting clozapine is 66.055 months. The data table also shows the value of b_1 (the gradient of the regression line) as -0.067. This value represents the change in the outcome associated with a unit change in the predictor, therefore for each extra month of age, the theoretical delay to clozapine is decreased by 0.067 months. The value of the regression coefficient (*b*) should be different from zero if the age of the patient has a significant impact on the ability of the model to predict the theoretical delay to clozapine use. This is tested using *t*-test, the results of which (and associated *p* values) are given in the final two columns of the table. The result of the first *t*-test is significant at a *p* value of < 0.0005. The result of the second *t*-test is non-significant at a *p* value of 0.074. The non-significant result for the *b* for the age of the patient means that this regression coefficients is not significantly different from zero, and so in the case of the age of the patient, this does not make a significant contribution ($p = 0.074$) to predicting the length of delay to clozapine initiation.

As explained previously, these data may not conform to normality assumptions and so I carried out bootstrapping procedures for the model parameters. The results from this are given in Appendix A (Table 7-22). The bootstrap confidence intervals indicate that the population value for *b* (the value of the regression coefficient) for the age of the patient is likely to fall between -0.126 and -0.011. As this interval does not include zero, there is a

genuine negative relationship between theoretical delay and the age of the patient in the population. Additionally, the significance associated with this confidence interval is $p = 0.016$, suggesting that there may be a significant relationship between the variables – but the result from the *t*-test described above contradicts this.

2.3.4.3 Multiple regression analysis

As outlined above, the two variables of age and duration of illness are likely to influence each other. The linear regression analysis showed that neither variable alone has an effect on the theoretical delay to clozapine initiation. However, the linear regression procedure does not control for the other potentially confounding variable when assessing the impact of the variable of interest on the outcome. Additionally, bootstrap confidence intervals for the relationship between the age of the patient and the theoretical delay to clozapine use suggested that there may be a significant correlation. In order to establish whether the combination of age and duration of illness affect the delay in clozapine prescribing, multiple regression analysis is required. Multiple regression analysis allows a model to be built that has several predictor variables; in this case, age and duration of illness.

As the linear regression showed that neither variable had an effect on the outcome, I did not use hierarchical (blockwise entry) to build the multiple regression models. I also did not use the stepwise method (automatic linear modelling), where the variables are entered into the model based on mathematical criterion, because of the risk of overemphasis of correlation of the two variables and over- or under-fitting the model. Instead, forced entry (putting both predictors into the model simultaneously) was appropriate as the data suggest that the influence of each variable on the outcome is the same.

For the first model, the predictor variable was the age of the patient. The second model used both the duration of the illness and the age of the patient as predictors. For both models, the dependent variable was the theoretical delay to clozapine prescription. The results from these models are presented in Appendix A (Table 7-23). The table shows the *R* value (the multiple correlation coefficients between the predictor and the outcome variable) for model

1, where only age was included as a predictor, to be 0.147. As expected, this is the same *R* as found in the simple linear regression calculated earlier. The R^2 for this variable is 0.532, which as explained previously is a measure of how much of the variability in the outcome is accounted for by the predictor. For this first model, the R^2 is 0.022, so the age of the patient accounts for 2.2% of the variation in the duration of the illness. However, when the other predictor of duration of illness is included in model 2, this value remains the same, at 0.022 or 2.2% of the variance in delay to clozapine use. Therefore, the inclusion of the new predictor of duration of illness explains none of the remaining 97.8% of the variation in the delay to clozapine prescription.

The model summary table also shows the adjusted R^2, and this gives an indication of the generalisability of the model. This value should ideally be as close as possible to the value of R^2. For model 1, the adjusted R^2 is 0.015, with the difference between the values being 0.007, or 0.7%. This means that if the model were derived from the whole population rather than the sample included in this study, then it would account for approximately 0.7% less variance in the outcome. The change statistics are explored further in the next columns in this table. The R^2 change column shows that model 1 causes R^2 to change from 0 to 0.022, and this change in the amount of variance explained results in an *F*-ratio of 3.238, which is not significant at a probability of 0.074. In model 2, where the duration of the illness has been added as a predictor, the R^2 does not change (the R^2 change is 0), so the R^2 of this model is 0.022. The *F*-ratio for this is 0.015, which is non-significant at a *p* of 0.902. Finally, the Durbin-Watson statistic is given in the last column of the table. This tests whether correlations exist between errors (or residuals) in the data. Violation of this assumption invalidates the confidence intervals and significance tests. In order for the assumption of independent errors to remain tenable, this value should be between 1 and 3 (and as close to 2 as possible). The value for this model is 1.740, showing that this assumption has been met.

I have so far presented the results from the one-way ANOVA for each continuous variable, which showed that neither age nor duration of illness have an effect on the delay to clozapine

use, although bootstrap confidence intervals for age hinted at a possibly significant negative relationship for this variable. I then combined these variables in a multiple regression analysis to establish their influence on the outcome variable when considered individually. This analysis suggested that the influence on the delay to clozapine use (if there is any significant influence) lies in the age, rather than the duration of illness of the patient. Both these continuous variables, having an influence on the dependent variable of delay to clozapine use, can be called covariates and therefore included in an analysis of covariance (ANCOVA). I am using the ANCOVA test here to eliminate the possibility of confounding of the results by either variable, as the test looks at the difference between the group means adjust for the covariates (age and duration of illness). The output data for the ANCOVA analyses are shown in Appendix A.

The first ANCOVA defines the dependent variable as the delay to clozapine use, the independent variable as the duration of the illness, and the covariate (the possible confounding variable) as the age of the patient at the point of clozapine initiation. The results for Levene's test of equality of error variances for this ANCOVA is presented in Appendix A (Table 7-24). Levene's test is significant at $p = 0.001$, indicating that the assumption of homogeneity of variances has been violated. However, the ANCOVA is a linear model, and so it is homogeneity of the residuals that matters, which is not tested by Levene's test. This is important to note however, and any significant results from the subsequent ANCOVA should ideally be bootstrapped to account for this.

The results table for the ANCOVA is shown in Appendix A (Table 7-25). From the significance values, it is evident that the covariate (age) has no significant effect on the outcome (theoretical delay), as the $p = 0.411$. When the effect of age is removed, the duration of illness also does not significantly affect the theoretical delay, at $p = 0.968$. Therefore, the theoretical delay is not influenced by the duration of the illness or by the age of the patient.

The second ANCOVA again uses the delay to clozapine treatment as the dependent variable, but this time the independent variable is set as the age of the patient, and the covariate

(confounding variable) as the duration of the illness. The results for Levene's test of equality of error variances for this ANCOVA is presented in Appendix A (Table 7-26). Levene's test is again significant at $p = 0.002$, indicating that the assumption of homogeneity of variances has been violated, but as discussed previously this may be of less importance as the ANCOVA is a linear test.

The results table for this ANCOVA is presented in Appendix A (Table 7-27). The significance values show that when duration of the illness is set as the covariate, it has no significant effect on the delay to clozapine use, at a p value = 0.806. The independent variable of age also has no effect on the outcome, at a p of 0.488. Removing the effect of the duration of illness from the age of the patient has no effect on the result, indicating no influence of age on the theoretical delay.

2.3.4.4 Gender

In order to establish the effects of the categorical variable of gender on the delay to clozapine prescribing, I used an independent samples *t*-test. The independent samples *t*-test expects (under the null hypothesis) that both samples (i.e. male and female patients) come from the same population, and therefore that their means (of delay to clozapine use) will be approximately equal. The results of the *t*-test for gender are given in Table 2-5.

Table 2-5 Independent samples t-test summary (gender)

		Statistic	**Bootstrap**			
			Bias	**Std. Error**	**BCa 95% Confidence Interval**	
					Lower	**Upper**
Male	*n*	102				
	Mean clozapine delay (months)	35.93	-0.20	4.18	28.52	43.60
	Std. Deviation	42.726	-0.719	5.162	33.031	50.975
	Std. Error Mean	4.231				
Female	*n*	47				
	Mean clozapine delay (months)	60.47	-0.26	9.06	43.99	78.19
	Std. Deviation	62.698	-1.058	6.614	49.958	72.314
	Std. Error Mean	9.145				

The table shows that men have a shorter mean delay to clozapine use than women. As the confidence intervals for the two groups do not overlap, this suggests that they may not be

from the same population.

The main test statistics for the independent samples *t*-test for gender are presented in Appendix A (Table 7-28). As discussed previously, Levene's test shows whether the variances are different between the different groups. Levene's test is significant for these data at $p < 0.0005$, therefore the assumption of homogeneity of variances has been violated and the test statistics in the row labelled 'equal variances not assumed' should be used. The mean difference between the groups is -24.537, with a standard error of the sampling distribution of differences of 10.077. The *t* statistic (calculated by dividing the mean difference by the standard error) is -2.435. The degrees of freedom (calculated by adding the two sample sizes and then subtracting the number of samples) is 66.408. The value of *t* is compared to the value of *t* expected if the null hypothesis is correct (that both the samples have the same mean), based on the calculated degrees of freedom. The value of *t* is 0.018, which is significant at $p < 0.05$. This shows that there is a significant difference in the mean delay to clozapine use when comparing male and female patients.

The results of the bootstrapping are also given in Appendix A (Table 7-29). The bootstrapping re-estimates the standard error of the mean difference, which is now estimated at 9.849 rather than 10.077. The difference between the means is -24.537, and the bootstrapped confidence interval for this ranges from -44.502 to -5.927. This confidence interval range is entirely negative and does not include zero. This shows that the true difference between the means is negative, and cannot be zero (i.e. the means are not the same). The bootstrap confidence interval therefore confirms the result outlined above; on average, females had a longer theoretical delay (mean = 60.47 months, SE = 9.15) than males (mean = 35.93 months, SE = 4.23). This difference, -24.54, BCa 95% CI [-44.502, -5.927] was significant $t(66.41) = -2.44$, $p = 0.018$.

2.3.4.5 Ethnicity

I used one-way ANOVA to examine the effect of the categorical variable of ethnicity on the theoretical delay to clozapine use. ANOVA analysis was required rather that the *t*-test used

for the categorical variable of gender described previously as the ethnicity variable contains more than two categories; the ANOVA is also a linear model, but allows the comparison of the means of more than 2 groups.

The descriptive statistics for the one-way ANOVA for the ethnicity variable are shown in Table 2-6. Black patients have a slightly higher mean delay than white patients, but the lowest mean delay is for patients in the ‘other’ ethnicity category.

Table 2-6 Descriptive statistics for one-way ANOVA (ethnicity)

				Bootstrap			
				Bias	**Std. Error**	**BCa 95% Confidence Interval**	
						Lower	**Upper**
White	*n*		61	0	6	51	71
	Mean clozapine delay (months)		43.75	0.38	7.10	29.62	59.24
	Std. Deviation		55.794	-0.713	7.515	39.681	68.521
	Std. Error		7.144				
	95% Confidence Interval for Mean	Lower Bound	29.46				
		Upper Bound	58.04				
	Minimum		0				
	Maximum		222				
Black	*n*		61	0	6	50	73
	Mean clozapine delay (months)		47.20	-0.46	6.29	35.95	57.85
	Std. Deviation		50.736	-1.372	6.000	39.651	58.459
	Std. Error		6.496				
	95% Confidence Interval for Mean	Lower Bound	34.20				
		Upper Bound	60.19				
	Minimum		0				
	Maximum		219				
Other	*n*		27	0	5	19	34
	Mean clozapine delay (months)		35.52	0.02	7.38	22.33	50.80
	Std. Deviation		39.613	-1.272	6.827	27.150	49.206
	Std. Error		7.624				
	95% Confidence Interval for Mean	Lower Bound	19.85				
		Upper Bound	51.19				
	Minimum		0				
	Maximum		153				
Total	*n*		149	0	0	0	0
	Mean		43.67	<0.005	4.08	35.69	51.86
	Std. Deviation		50.975	-0.468	4.195	43.212	57.433
	Std. Error		4.176				
	95% Confidence Interval for Mean	Lower Bound	35.42				
		Upper Bound	51.92				
	Minimum		0				
	Maximum		222				

Next, Levene's test of the difference in variance between the three groups is shown in Appendix A (Table 7-30). The test is non-significant at a *p* of 0.486, showing that the homogeneity of variances can be assumed and there is no requirement to transform the data.

The ANOVA output data table is presented in Appendix A (Table 7-31). The data are divided into between groups effects, which are the effects due to the model (the experimental effects)

and the within-group effects, which are the effects due to unsystematic variation of the data. For the between groups effect, the sum of squares is 2553.194, with a degrees of freedom of 2, and a mean square of the model of 1276.597. The sum of squares and mean squares represent the experimental effect. The within groups model has a sum of squares (the residual sum of squares, as it corresponds to the amount of unsystematic variation in the data) of 382023.692, and a mean square of 2616.601 (the average amount of unsystematic variation). The *F*-ratio shows whether the group means are the same. The ratio is 0.488, with a significance of 0.615 (this significance is the probability of calculating an *F* ratio this size if there was no difference between the means in the populations). This significance shows that there is a 61.5% chance that the *F* ratio would be calculated if in reality there was no effect. As this significance is > 0.05, the ANOVA shows that there is no difference in the means between the different ethnicity categories.

As I had no specific hypothesis that any particular ethnicity category would be expected to have an effect on the theoretical delay to clozapine use, I carried out *post-hoc* tests to compare all the groups of participants with each other. The results of Tukey's test (known as Tukey's Honestly Significant Difference, or HSD), Gabriels' pairwise test procedure and the Games-Howell procedure are shown in Appendix A (Table 7-32). Tukey's test controls for type 1 errors, and is used because I have no reason to think that the population variances are unequal. For this test, each group participant is compared to all the remaining groups, as can be seen in the table. For each pair of groups, the difference between the means, the standard error of the difference, the significance level of the difference and the 95% confidence intervals are given. For all comparisons, the differences between the means are non-significant at $p > 0.05$. I have used Gabriel's pairwise test procedure as the sample sizes in the three categories are different. It again controls for type 1 errors and as for Tukey's HSD, finds that the differences between the means for each pair group are non-significant. Finally, the Games-Howell procedure is the most powerful test of the three presented, and supports the other results in also finding no significant differences between the group means. Overall, there was no significant effect of ethnicity on theoretical delay to clozapine, $F(2, 146) = 0.688$, $p = 0.505$.

2.3.4.6 Diagnosis

I applied the same procedures to analysis of the effect of diagnosis on the theoretical delay to clozapine, as similarly to ethnicity, this variable contained more than 2 categories. The descriptive statistics for the one-way ANOVA for the diagnosis variable are shown in Table 2-7.

Table 2-7 Descriptive statistics for one-way ANOVA (diagnosis)

				Bootstrap			
				Bias	Std. Error	BCa 95% Confidence Interval	
						Lower	Upper
Schizophrenia	*n*		116	0	5	106	125
	Mean clozapine delay (months)		41.94	0.15	5.13	32.56	52.53
	Std. Deviation		52.830	-0.255	5.406	42.050	62.614
	Std. Error		4.905				
	95% Confidence Interval for Mean	Lower Bound	32.22				
		Upper Bound	51.66				
	Minimum		0				
	Maximum		222				
Schizoaffective disorder	*n*		24	0	4	16	32
	Mean clozapine delay (months)		41.21	0.28	8.11	27.44	57.69
	Std. Deviation		39.715	-1.110	6.960	27.315	49.806
	Std. Error		8.107				
	95% Confidence Interval for Mean	Lower Bound	24.44				
		Upper Bound	57.98				
	Minimum		0				
	Maximum		153				
Other	*n*		9	0	3	5	14
	Mean clozapine delay (months)		72.56	-0.32	16.78	45.37	107.05
	Std. Deviation		49.156	-5.456	13.800	25.195	61.362
	Std. Error		16.385				
	95% Confidence Interval for Mean	Lower Bound	34.77				
		Upper Bound	110.34				
	Minimum		14				
	Maximum		176				
Total	*n*		149	0	0	0	0
	Mean clozapine delay (months)		43.67	0.14	4.30	35.80	52.36
	Std. Deviation		50.975	-0.117	4.414	42.175	59.139
	Std. Error		4.176				
	95% Confidence Interval for Mean	Lower Bound	35.42				
		Upper Bound	51.92				
	Minimum		0				
	Maximum		222				

Table 2-7 shows that the mean theoretical delay to clozapine use was longest for those with a diagnosis in the 'other' category. Patients with schizoaffective disorder had the shortest delay.

Next, Levene's test of the difference in variance between the three groups is shown in Appendix A (Table 7-33). The test is non-significant at a *p* of 0.452, showing that the homogeneity of variances can be assumed and there is no requirement to transform the data.

The ANOVA output data table is presented in Appendix A (Table 7-34). The F-ratio is 1.551, with a significance of 0.215. This significance shows that there is a 21.5% chance that the *F* ratio would be calculated if in reality there was no effect. As this significance is > 0.05, the ANOVA shows that there is no difference in the means between the different diagnosis categories.

As for the ethnicity variable described previously, I carried out *post-hoc* tests for the diagnosis variable to compare all the groups of participants with each other. The results of Tukey's test, Gabriels' pairwise test procedure and the Games-Howell procedure are shown in Appendix A (Table 7-35). All three tests found no significant differences between the group means at $p > 0.05$. Overall, there was no significant effect of diagnosis on theoretical delay to clozapine, $F(2, 146) = 1.608$, $p = 0.226$.

2.4 Summary

This study retrospectively examined the clinical notes of patients commencing clozapine over a 4 year period at SLaM to establish antipsychotic prescribing histories before clozapine was prescribed. In total, 149 patients were included in the analysis and 75 were excluded. Patients were excluded from the data analysis where their prescribing histories could not be established from the clinical notes. Excluded patients tended to be older, and this difference, -8.764, BCa 95% CI [-12.217, -5.379] was significant $t(217) = -5.436$, $p = <0.0001$). Excluded patients also tended to have a longer duration of illness, and this difference, -7.837 BCa 95% CI [-10.00, -5.752] was significant $t(217) = -6.612$, $p < 0.0001$. Gender also affected the likelihood of being excluded from the analysis (χ^2 (1) = 4.917, $p = 0.027$), with male patients being more likely to be included in the study, with an odds ratio of 1.90. The ethnicity of patients also differed significantly between the included and excluded groups (χ^2 (2) = 7.333, $p = 0.026$), with the excluded patient group made up of a higher proportion of white patients

and a lower proportion of black patients than the included group. There was also a significant difference in diagnosis across the two groups (χ^2 (2) = 8.808, p = 0.012), with patients 3.71 times more likely to be excluded from the analysis if they had a diagnosis other than schizophrenia or schizoaffective disorder. Overall, excluded patients were more likely to be older, have a longer duration of illness, be female, white, and have a diagnosis of something other than schizophrenia or schizoaffective disorder.

I found a mean theoretical delay to clozapine prescription of 43.38 months (3.6 years, SE = 4.18 months). This delay was not influenced by the duration of the psychotic illness or the age of the patient. Gender did have an effect on the delay to clozapine use, with female patients having a longer theoretical delay (mean = 60.47 months, SE = 9.15) than male patients (mean = 35.93 months, SE = 4.23). This difference, -24.54, BCa 95% CI [-44.502, -5.927] was significant t(66.41) = -2.44, p = 0.018. The ethnicity of the patient had no effect on the delay to clozapine (F(2, 146) = 0.688, p = 0.505), and neither did the diagnosis (F(2, 146) = 1.608, p = 0.226).

2.5 Publications arising from this study

See Appendix I: Oliver Howes, Francis Vergunst, **Siobhan Gee**, Philip McGuire, Shitij Kapur, David Taylor (2012) Adherence to treatment guidelines in clinical practice: a study of antipsychotic prescription prior to clozapine initiation. *British Journal of Psychiatry*, 201:481-485.

3 Practitioner attitudes to clozapine initiation

3.1 Introduction

Despite clear recommendations for the use of clozapine, I have shown in chapter 2 that patients experience lengthy delays in prescribing. In 2001, the mean theoretical delay to clozapine prescribing (the time from the end of the second failed antipsychotic trial, after which clozapine should be initiated, to the time when clozapine was actually started) was 5 years (71). At the same Trust in 2010, this delay had reduced but still stood at almost 4 years (148).

At the time of the 2001 study, several possible reasons for the prescribing delays were suggested; patient reluctance to comply with blood tests, clinician fears over probable non-compliance with medication or the development of agranulocytosis or other side effects, cost, lack of experience in prescribing clozapine, and lack of clinician confidence in the clinical effectiveness of clozapine in treatment-resistant schizophrenia. These theories were not tested at the time.

This study aims to clarify the barriers to prescribing of clozapine in treatment-resistant schizophrenia where clozapine initiation is indicated, as perceived by clinicians directly involved in the care of such patients.

3.1.1 Objectives

- To establish how familiar clinicians feel with clozapine prescribing guidelines and procedures.
- To investigate how effective clinicians feel clozapine is, compared with other antipsychotics.
- To elucidate factors clinicians feel are likely to delay prescribing clozapine.
- To elucidate factors clinicians feel are likely to reduce the delay to prescribing clozapine.
- To examine differences in the above outcome measures between professional groups.

3.2 Method

A questionnaire suitable for electronic and hard-copy completion was formulated and piloted to a convenience sample of 10 members of pharmacy staff, following which questions were refined (Appendix B). The questionnaire was made available electronically for all staff at SLaM to complete. An advertisement was run in the weekly staff news bulletin, and emailed to all clinical team leaders and consultants in the Trust, requesting they pass this on to their team members. All inpatient and outpatient team leaders were further contacted by phone to explain the study, and provided with paper copies of the questionnaire. In this way all members of clinical staff in the Trust had an equal chance of response and therefore selection into the sample, keeping sampling error to a minimum. The questionnaire was available electronically and in paper format over a 12 month period, allowing for rotation of junior doctor staff into and out of the Trust. Team leaders were contacted twice after the initial call – once to confirm receipt of the electronic and paper questionnaires, and finally after allowing time for completion to encourage further responses. Further, teaching sessions for junior doctors were directly provided with paper copies of the questionnaire. Making the questionnaire available as widely as possible both electronically and in paper format increased convenience for responders, with an aim of increasing response rate. It is however the case that this limited the scope for prompting or probing for further responses or clarification, although free text comment options were provided.

The questionnaire was completed anonymously and demographic data collected:

- Professional status
- Main ward/community location
- Gender
- Age bracket

Firstly, practitioners were asked to declare how familiar they were with the NICE schizophrenia guidelines (not at all/a little/fairly/very familiar):

> ‘How familiar are you with the NICE guidelines relating to treatment-resistant schizophrenia?’

Beliefs about the relative effectiveness of clozapine compared to other antipsychotics were explored using a 10 point Likert scale with a visual prompt, ranging from ‘much less effective’ to ‘much more effective’:

> ‘How would you rate clozapine’s effectiveness in treating schizophrenia compared with other antipsychotics?’

Practitioners were asked directly about their clinical practice in clozapine initiation (without a direct prompt that their response may or may not adhere to guidelines):

> ‘When would you typically consider authorising/supporting the initiation of clozapine treatment?’

Options for response to this question were:

- As first line treatment
- After one adequate antipsychotic trial
- After two adequate antipsychotic trials
- After three adequate antipsychotic trials
- After four or more adequate antipsychotic trials

Secondly, the familiarity of practitioners with the process of clozapine initiation was investigated. Clozapine requires more pre-treatment testing and administration processes than any other available antipsychotic, necessitating full blood count testing, registration with a centralised data base for the patient, prescriber and pharmacy, as well as on-going monitoring and communication with the supplying company. Questionnaire respondents were asked:

> ‘How familiar are you with methods for the initiation of clozapine treatment?’ (not at all/a little/fairly/very familiar)

‘Approximately how many patients currently under your care are receiving clozapine?’ (free text answer)

‘I have been responsible for authorising/supporting clozapine initiation and titration…’

- Within the last 6 months
- Within the last year
- More than a year ago
- Never

Thirdly, patients themselves are frequently cited by staff as being the main reason for non-prescription of clozapine. The beliefs of clinicians about patient experiences with clozapine were investigated:

‘In terms of treatment satisfaction, how satisfied do you believe patients treated with clozapine are, compared with patients treated with other (atypical) antipsychotics?’

- much less satisfied
- somewhat less satisfied
- somewhat more satisfied
- much more satisfied

I asked respondents to rate the following ‘patient factors’ on their likelihood to lead to delays in the initiation of clozapine. Response options were: infrequently/somewhat frequently/fairly frequently/very frequently/don’t know:

- Refusal / reticence about obtaining baseline blood tests
- Refusal / reticence about regular blood monitoring
- Refusal / reticence due to need for hospital admission for titration
- Patient unconvinced about clozapine’s efficacy
- Patient concerned about tolerability
- Significant medical factors / complications

Practitioners were asked to rate the following factors on their likelihood to delay prescribing, again with response options of: infrequently/somewhat frequently/fairly frequently/very frequently/don't know. Included in this question set were barriers that come from the clinician themselves regarding concerns around potential tolerability or medical complications.

- Administrative (e.g. Time taken to register the patient with a clozapine monitoring service)
- Obtaining baseline blood tests
- Staff resources (e.g. Lack of staff to monitor clozapine)
- Need for hospital admission (e.g. Delays in obtaining an admission)
- Cost of clozapine medication
- Concerns about tolerability
- Significant medical factors / complications

In order to evaluate opinion on the usefulness of additional administrative or clinical help in initiating clozapine, respondents were asked directly:

> 'In your team, would additional clinical and/or administrative resources facilitate the initiation of clozapine?' (Yes/No)

Respondents were also asked to rate the following factors in terms of helpfulness (not helpful/somewhat helpful/fairly helpful/very helpful/don't know):

- Additional administrative support (e.g. patient registration)
- Additional staff dedicated to obtaining baseline blood tests
- Dedicated hospital beds to enable initiation of clozapine as an inpatient
- Dedicated staff to arrange and monitor the initiation of clozapine as an out-patient
- Dedicated day-hospital placements to initiate clozapine as an outpatient

Finally, I was interested in the relationship between staff perception of the scale of under-prescribing of clozapine as compared to the reality demonstrated in my previous study. Participants were asked:

'Approximately what percentage of patients under your care who are eligible for clozapine are not currently receiving clozapine?'

- 0 – 20%
- 21 – 40%
- 41 – 60%
- 61 – 80%
- 81 – 100%

3.2.1 Statistical analysis

Data were analysed using Microsoft Excel 2010 and IBM SPSS Statistics 21. Responses from doctors (trainee psychiatrists and consultant psychiatrists combined) and pharmacy staff (pharmacists, pharmacy technicians and pre-registration pharmacists combined) were compared using the Wilcoxon-Mann-Whitney two-sample rank-sum test. This test describes the shape of the distribution of scores in each group by ranking the data; the lowest score is given a rank of 1, the next highest a rank of 2, and so on. In this way, the effect of outlying results is eliminated as all the analysis is carried out on the ranked position of the data, rather than the actual scores. Higher mean ranks are equivalent to higher mean scores in the original data, and so the professional group with the highest mean rank will be the group that contains the greatest number of high scores from the questionnaire responses. The Mann-Whitney test statistic, *U*, is calculated using the sample sizes of the two groups, and the sum of the ranks for the first group. It is directly related to Wilcoxon test statistic, *W*, and the two can be used interchangeably. The *z*-score is calculated from the test statistic, the mean of the test statistic, and the standard error. Finally, the asymptotic significance is given which is the probability of the test statistic of the magnitude calculated or above occurring if there were no difference between the two groups (the null hypothesis).

3.3 Results

In total, 144 responses were received, the majority of which were from females (58%, *n* = 83). The most commonly represented age group was between 26 and 35 years (47%, *n* = 68). At the time of sampling the majority of practitioners worked predominantly in inpatient areas (63%, *n* = 91). Doctors were the most frequent responders (trainee psychiatrists, 42%, *n* = 60; consultant psychiatrists, 14%, *n* = 20), followed by members of pharmacy staff (16%, *n* = 23). The distribution of respondents is shown in Table 3-1. There was no forced function to answer all questions, and so the results reflect some degree of attrition of respondents throughout the questionnaire. Responses to free-text questions are given in Appendix D.

Table 3-1 Demographics of questionnaire respondents

	n	**%**
Gender		
Female	83	58
Male	60	42
Not answered	1	1
Age		
18-25 years	6	4
26-35 years	68	47
36-45 years	40	28
46-55 years	24	17
56+ years	4	3
Not answered	2	1
Professional title		
Care coordinator	2	1
Consultant psychiatrist	20	14
Nurse	26	18
Occupational therapist	1	1
Pharmacy staff	23	16
Psychologist	4	3
Social worker	7	5
Trainee psychiatrist	60	42
Other	1	1
Main working location		
Inpatient	91	63
Outpatient	36	25
Unknown	17	12

Table 3-2 Answers to questionnaire: factors likely to delay clozapine initiation

	Not frequently % (*n*)	Somewhat frequently % (*n*)	Fairly frequently % (*n*)	Very frequently % (*n*)	Don't know % (*n*)	*n*
In your opinion, how frequently do the following patient factors lead to delays in the initiation of clozapine once clozapine treatment is indicated?						
Refusal/reticence about obtaining baseline blood tests	14 (18)	29 (37)	33 (42)	23 (30)	1 (1)	128
Refusal/reticence about regular blood monitoring	9 (11)	27 (34)	31 (40)	34 (43)	0 (0)	128
Refusal/reticence due to need for hospital admission for titration	26 (33)	22 (28)	18 (23)	14 (17)	19 (24)	125
Patient unconvinced about clozapine's efficacy	29 (37)	32 (41)	23 (30)	7 (9)	9 (11)	128
Patient concerned about tolerability	24 (31)	25 (32)	34 (44)	12 (15)	5 (6)	128
Significant medical factors/complications	23 (29)	36 (46)	23 (30)	14 (18)	4 (5)	128
How frequently do the following factors delay you from initiating/supporting clozapine titration in patients eligible for treatment?						
Administrative (e.g. time taken to register with monitoring scheme)	57 (69)	19 (23)	11 (13)	2 (3)	11 (13)	121
Obtaining baseline blood tests	36 (43)	34 (40)	15 (18)	7 (8)	8 (10)	119
Staff resources (e.g. lack of staff to monitor clozapine)	59 (71)	11 (13)	12 (14)	10 (12)	8 (10)	120
Need for hospital admission (e.g. delays in obtaining an admission)	40 (48)	13 (15)	13 (15)	7 (8)	28 (33)	119
Cost of clozapine medication	82 (99)	1 (1)	1 (1)	0 (0)	17 (20)	121
Concerns about tolerability	35 (42)	33 (40)	20 (24)	7 (8)	6 (7)	121
Significant medical factors/compliance	21 (25)	36 (44)	24 (29)	13 (16)	6 (7)	121

Data are shown as percentage of respondents who answered each question

Table 3-2 shows that patient factors were most often nominated as ‘very’ or ‘fairly’ frequently leading to delays in the initiation of clozapine – either refusal/reticence about obtaining baseline or regular blood tests. Factors most often chosen as ‘not’ frequently leading to delays in clozapine initiation were the need for hospital admission for titration of clozapine, or patients being unconvinced of the efficacy of clozapine. A lack of resources for monitoring clozapine was the factor most often chosen as likely to delay clozapine initiation, with staff concerns about tolerability, comorbid medical factors, or compliance ‘fairly’ frequently being an issue. The cost of clozapine was clearly not an issue, with the majority of respondents feeling this way.

Table 3-3 Answers to questionnaire: factors likely to aid access to clozapine

	Not helpful % (*n*)	Somewhat helpful % (*n*)	Fairly helpful % (*n*)	Very helpful % (*n*)	Don't know % (*n*)	*n*
In your opinion, how helpful would the following factors be in terms of facilitating the initiation of clozapine, were they available?						
Additional administrative support (e.g. patient registration)	22 (26)	32 (38)	24 (28)	15 (18)	7 (8)	118
Additional staff dedicated to obtaining baseline blood tests	15 (18)	28 (33)	27 (32)	27 (32)	3 (3)	118
Dedicated hospital beds to enable initiation of clozapine as an inpatient	17 (20)	25 (29)	18 (21)	26 (30)	15 (17)	117
Dedicated staff to arrange and monitor the initiation of clozapine as an outpatient	11 (13)	18 (21)	24 (28)	40 (47)	8 (9)	118
Dedicated day-hospital placements to initiate clozapine as an outpatient	12 (14)	21 (25)	21 (24)	38 (45)	8 (9)	117

Data are shown as percentage of respondents who answered each question

Table 3-3 shows that factors nominated as 'very helpful' by responders to the survey were dedicated staff to initiation clozapine as an outpatient, and day-hospital placements for the same. Dedicated inpatient beds were also thought likely to be helpful, as were staff focussed on obtaining baseline blood tests. Extra administrative support for patient registration appeared likely to be less helpful.

3.3.1 Perceived familiarity with guidelines

Self-perceived familiarity with the UK NICE schizophrenia guidelines was high, with 81% (*n* = 113 of 140 respondents) stating that they were 'fairly' (45%, *n* = 63) or 'very' (36%, *n* = 50) familiar with the guidance (Figure 3-1).

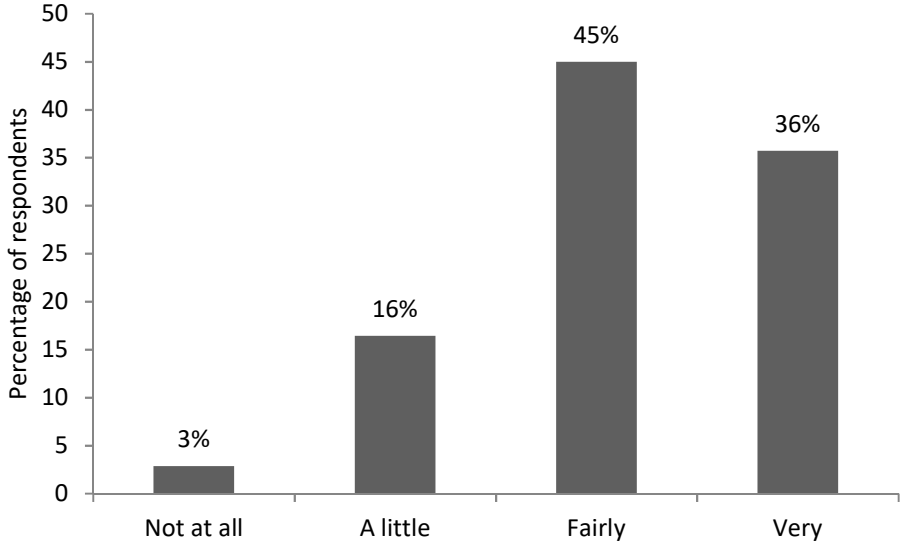

Figure 3-1 Responses to 'how familiar are you with the NICE guidelines relating to treatment-resistant schizophrenia?'

Nearly half (48%, *n* = 69 of 143 respondents) were also 'very familiar' with the methods of initiation of clozapine (Figure 3-2), with 56% (*n* = 79 of 141 respondents) stating that they had been responsible for authorising or supporting the initiation of clozapine therapy in the preceding six months. A significant minority however (14%, *n* = 20) had 'never' done so (Figure 3-3). Psychiatrists stated they had a median of 1 patient (range = 0 – 40, IQR = 6) currently under their care who was receiving clozapine.

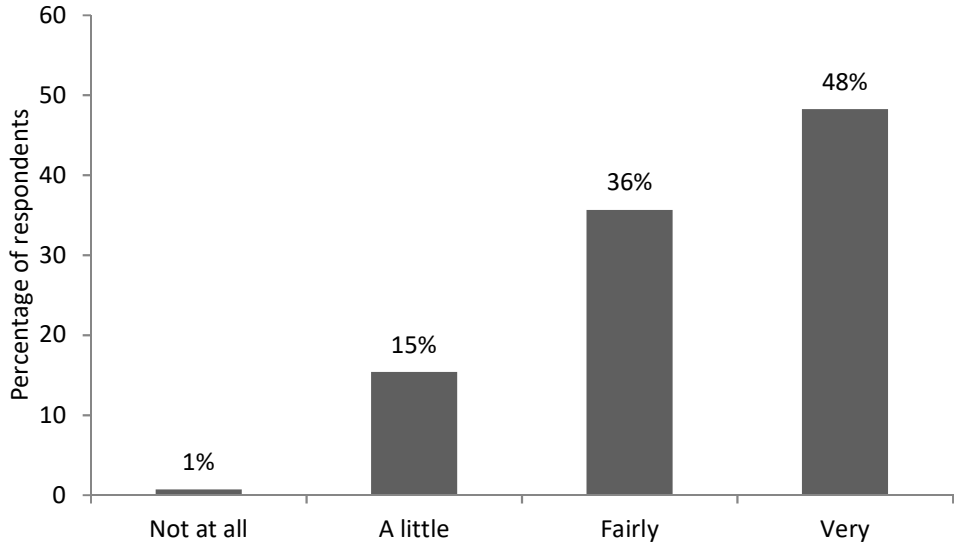

Figure 3-2 Responses to 'How familiar are you with methods for the initiation of clozapine treatment?'

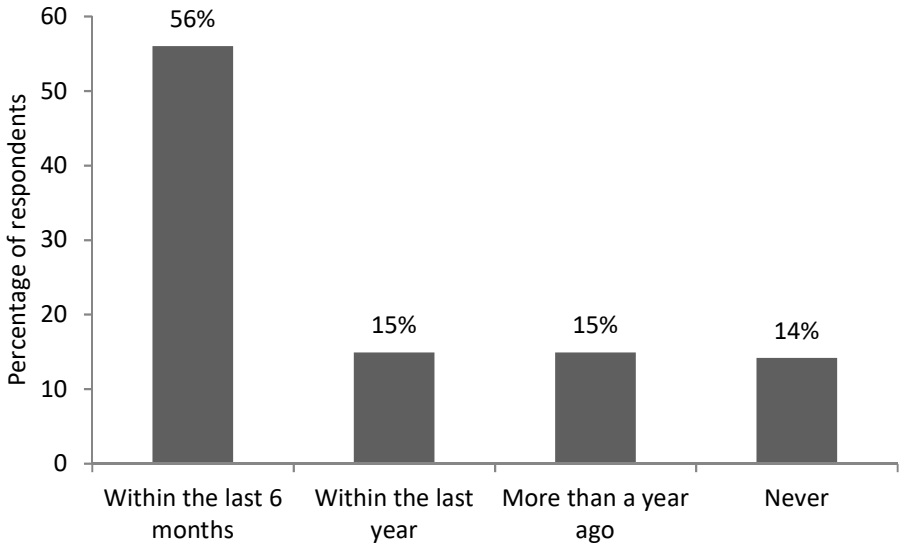

Figure 3-3 Responses to 'I have been responsible for authorising/supporting clozapine initiation and titration…'

3.3.2 Opinions of clozapine effectiveness

When asked to rate the relative effectiveness of clozapine in treating schizophrenia on a 1 to 10 Likert scale (1 indicating 'much less effective', 5 being 'about the same', and 10 'much more effective' than other antipsychotics), the mode of the scores given was 8 (range 1 to 10, median = 8) (Figure 3-4).

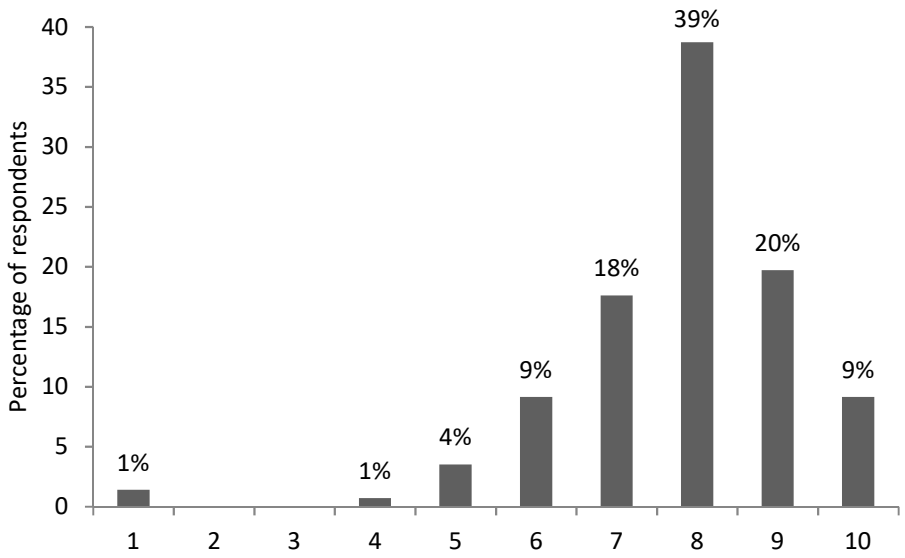

Figure 3-4 Responses to 'how would you rate clozapine's effectiveness in treating schizophrenia compared with other antipsychotics?'

Most (71%, *n* = 96 of 135 respondents) felt that patients were 'somewhat more satisfied' with clozapine treatment, compared with patients treated with other atypical antipsychotics. However, 19% (*n* = 25) thought that clozapine-treated patients are 'somewhat less satisfied' than their counterparts on atypical drugs (Figure 3-5).

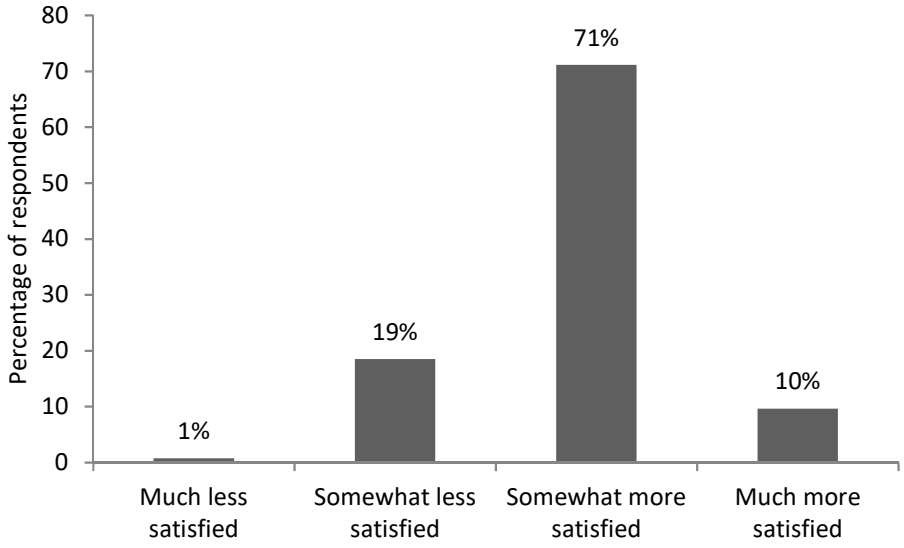

Figure 3-5 Responses to 'In terms of treatment satisfaction, how satisfied do you believe patients treated with clozapine are, compared with patients treated with other (atypical) antipsychotics?'

The majority (78%, *n* = 105 of 134 respondents) of responders stated that they would consider authorising or supporting the initiation of clozapine after two adequate antipsychotic trials had failed. A minority (14%, *n* = 19) would wait until three antipsychotics had been tried, 3% (*n* = 4) would postpone until the fourth antipsychotic had failed, and 4% (n = 4) would give clozapine after one adequate trial of another antipsychotic (Figure 3-6).

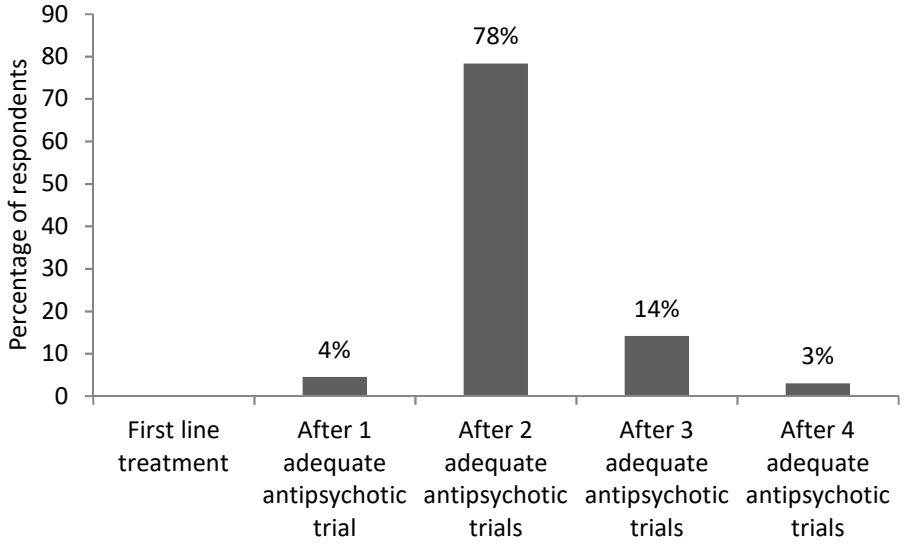

Figure 3-6 Responses to 'When would you typically consider authorising/supporting the initiation of clozapine treatment?'

Overall 35% (*n* = 50 of 143 respondents) of responders thought that between zero and 20% of their patients who were not receiving clozapine would be eligible to do so, and the same proportion stated that they didn't know how many of their patients were not prescribed clozapine where it would be indicated (Figure 3-7).

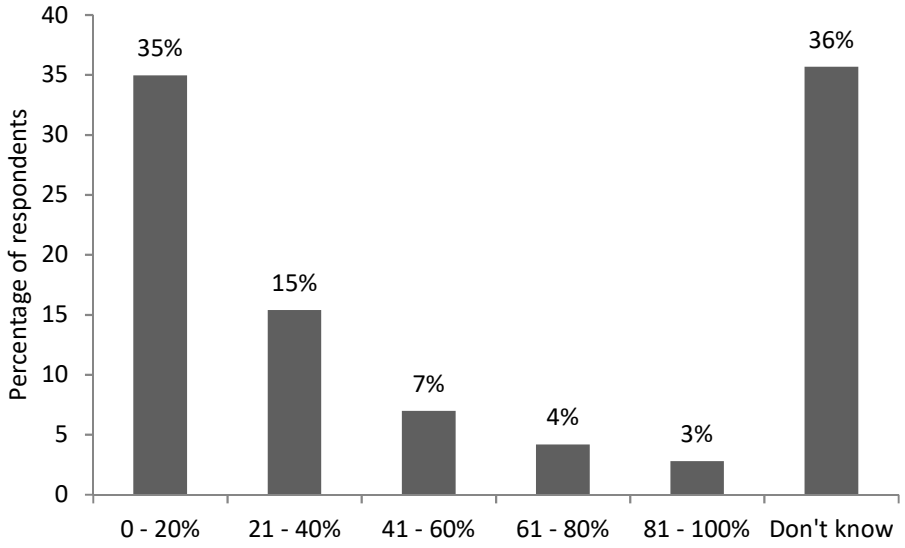

Figure 3-7 Responses to 'Approximately what percentage of patients under your care who are eligible for clozapine are not currently receiving clozapine?'

3.3.3 Factors influencing clozapine delay

Practitioners were asked how frequently they thought a range of factors were responsible for delays in the initiation of clozapine, once treatment was indicated. Figure 3-8 presents the results, shown as the percentage of respondents who indicated that the factor restricts the use of clozapine 'fairly' or 'very' frequently. The factors most frequently chosen as 'very' or 'fairly' restrictive to clozapine use were patient refusal or reticence regarding baseline or ongoing blood tests, with more than 50% of respondents for each of these factors feeling this way. The cost and administrative burden of clozapine were least likely to be nominated as very or fairly often barriers to clozapine initiation.

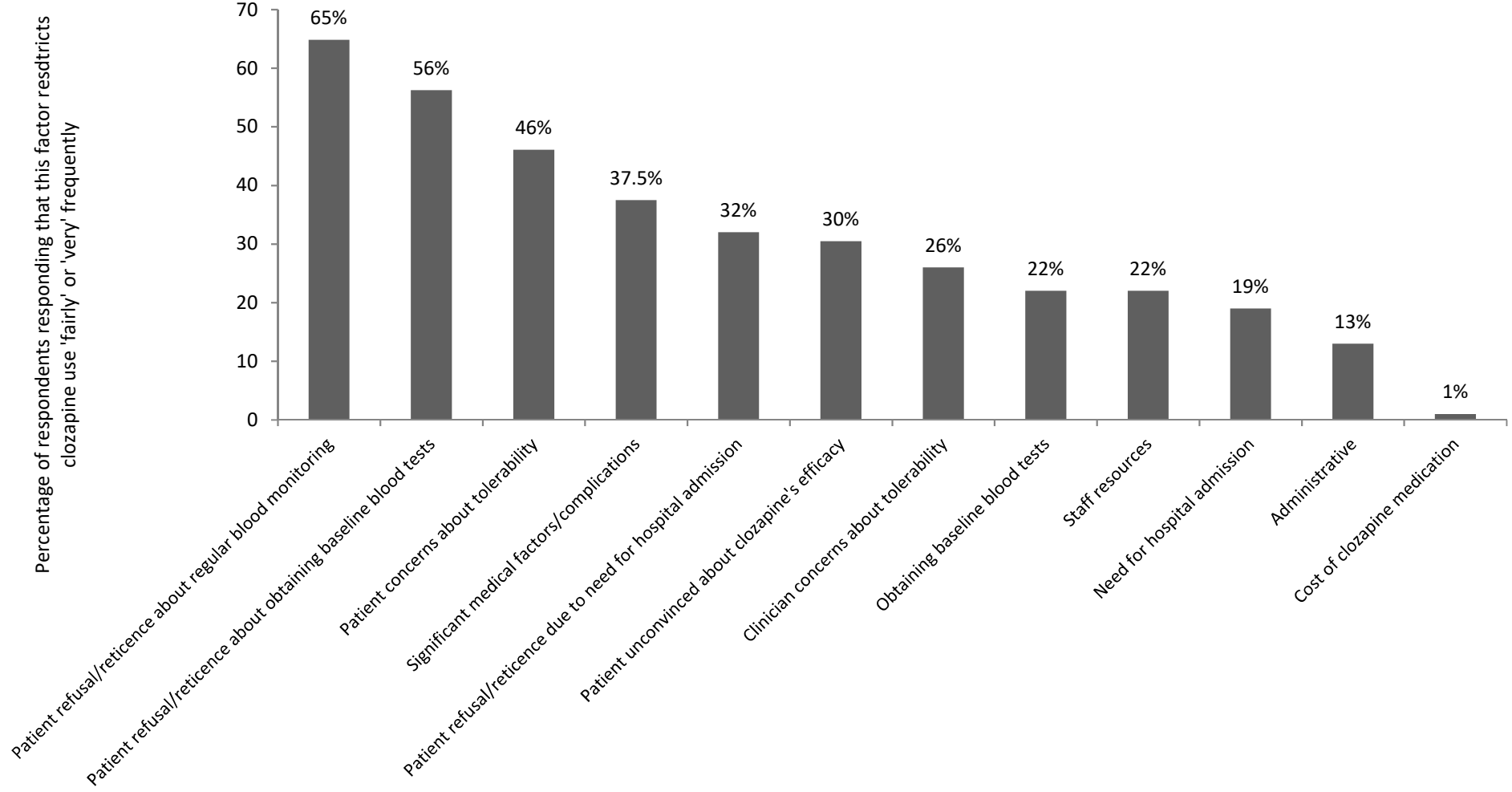

Figure 3-8 Responses to 'How frequently do the following factors delay you from initiating/supporting clozapine titration in patients eligible for treatment

3.3.4 Factors that reduce delays to clozapine initiation

Practitioners were asked how frequently they thought a range of factors would help facilitate the initiation of clozapine, were they available. The results are presented in Figure 3-9. Dedicated staff for outpatient clozapine initiation, obtaining baseline blood tests, and day hospital placements specifically for this purpose, were felt by more than half of respondents to be 'very' or 'fairly' helpful for increasing clozapine initiation.

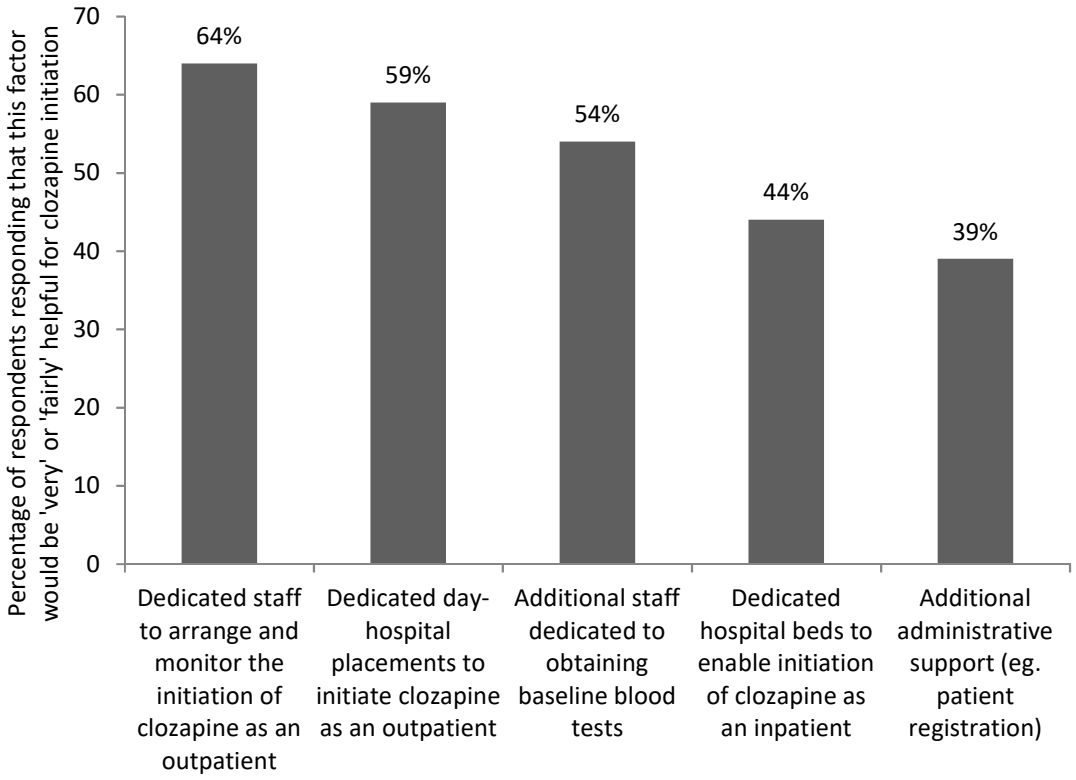

Figure 3-9 Responses to 'How helpful would the following factors be in terms of facilitating the initiation of clozapine, were they available?'

3.3.5 Comparison by profession

Members of pharmacy staff declared better familiarity with the use of clozapine than other professionals; 68% (*n* = 15 of 22 respondents) were 'very' familiar with the NICE schizophrenia guidelines, compared with 27% (*n* = 21 of 79 respondents) of medical staff, and 36% (*n* = 14 of 39 respondents) from other professional groups (Figure 3-10).

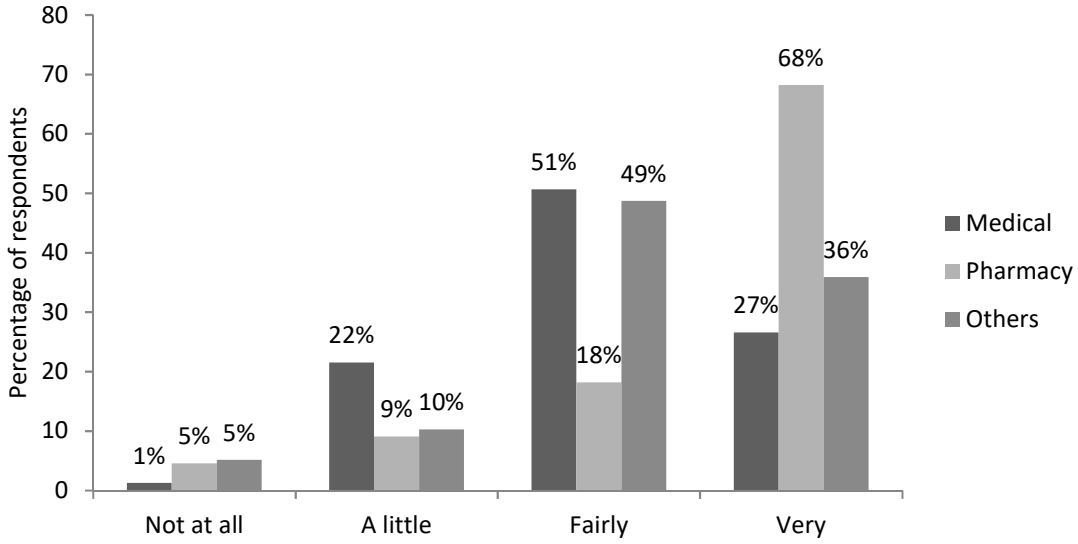

Figure 3-10 Responses to 'How familiar are you with the NICE guidelines relating to treatment resistant schizophrenia?'

A similar response pattern was evident when asked how familiar respondents were with the methods for the initiation of clozapine, with 74% (*n* = 17 of 23 respondents) of pharmacy staff feeling 'very familiar' with the process, representing the majority of responses for this professional group (Figure 3-11). The most frequently selected response from medical staff was 'fairly familiar' (44%, *n* = 40 of 80 respondents).

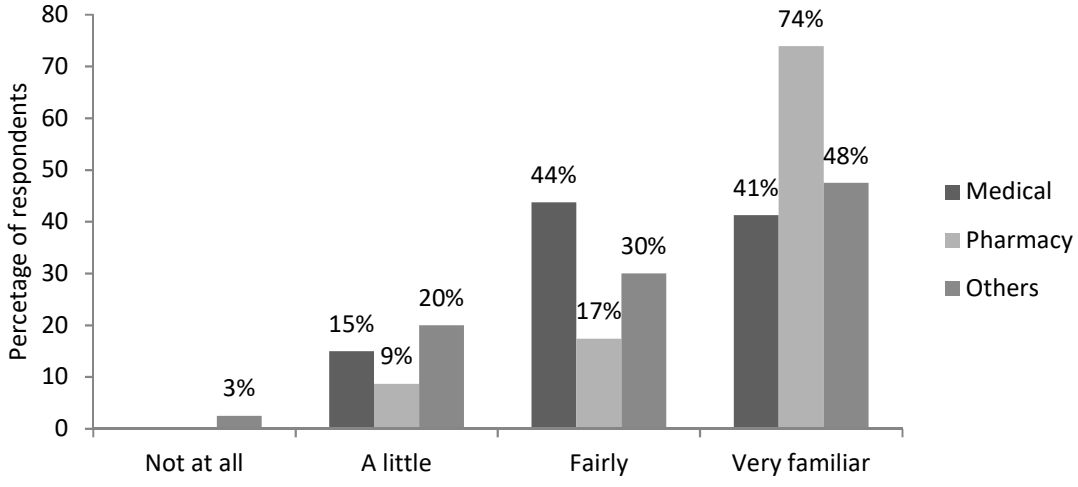

Figure 3-11 Responses to 'How familiar are you with methods for the initiation of clozapine treatment?'

When asked to rate clozapine's effectiveness compared with other atypical antipsychotics, pharmacy staff gave the highest scores (mean 8.2, SD = 1.1), doctors slightly lower (mean 7.9, SD = 1.4) and other professionals the lowest (mean 7.4, SD = 1.7) (Figure 3-12).

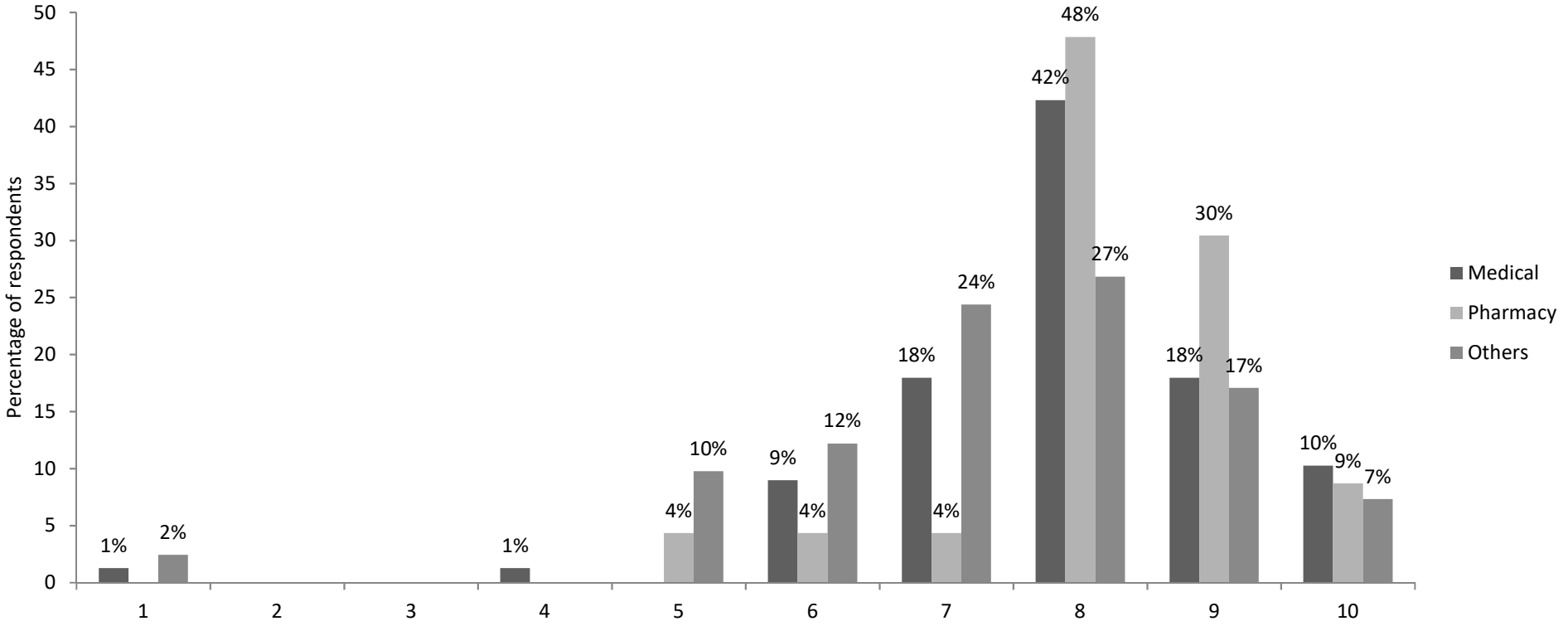

Figure 3-12 Responses to 'how would you rate clozapine's effectiveness in treating schizophrenia compared with other antipsychotics?'

This is also reflected in professionals' opinions of patient satisfaction with treatment; whilst the majority of all professionals thought patients were 'somewhat more satisfied' with clozapine treatment than other antipsychotics, both doctors and other health professionals gave a wider spread of results – 20% (n = 15 of 74 respondents) and 21% (*n* = 8 of 38 respondents) respectively thought patients were 'somewhat less satisfied', compared with just 9% (*n* = 2 of 23 respondents) of pharmacy staff (Figure 3-13).

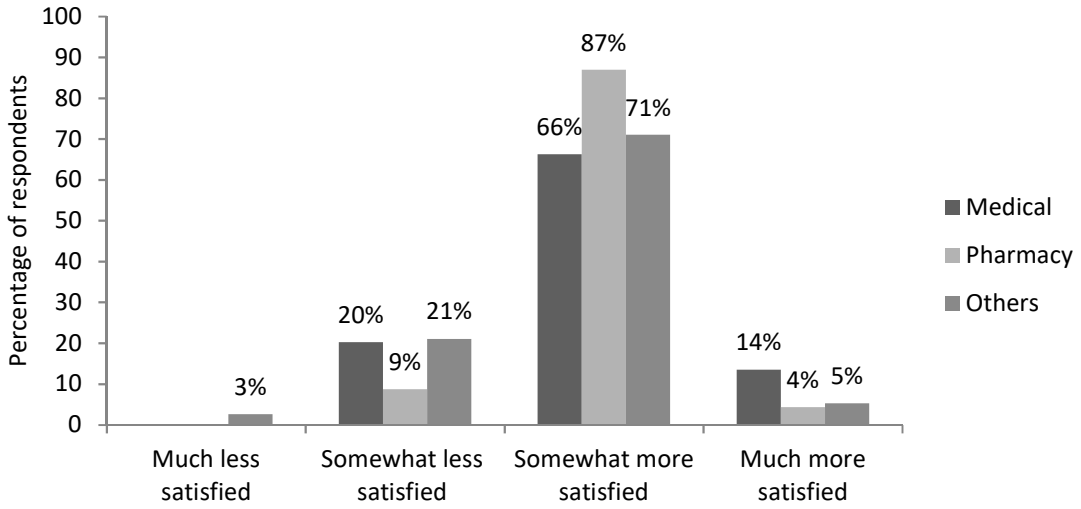

Figure 3-13 Responses to 'In terms of treatment satisfaction, how satisfied do you believe patients treated with clozapine are, compared with patients treated with other (atypical) antipsychotics?'

Table 3-4 Mann-Whitney test ranking for clozapine familiarity and effectiveness questions

	Professional status	***n***	**Mean Rank**	**Asymp. Sig. (2-tailed)**
How familiar are you with the NICE guidelines relating to treatment resistant schizophrenia?	Doctor	79	46.80	0.003
	Pharmacy staff	22	66.07	
	Total	101		
How familiar are you with methods for the initiation of clozapine treatment?	Doctor	80	48.38	0.012
	Pharmacy staff	23	64.59	
	Total	103		
How would you rate clozapine's effectiveness in treating schizophrenia compared with other antipsychotics?	Doctor	78	49.08	0.201
	Pharmacy staff	23	57.52	
	Total	101		
In terms of treatment satisfaction, how satisfied do you believe patients treated with clozapine are, compared with patients treated with other (atypical) antipsychotics?	Doctor	74	48.69	0.806
	Pharmacy staff	23	50.00	
	Total	97		

Table 3-4 demonstrates that pharmacy staff allocated higher scores to all questions than medical staff, shown by higher mean ranks in the first results column. The data show (see also Table 7-36 in Appendix C) that the distributions in the two groups differed significantly

for familiarity with the NICE schizophrenia guidelines (U = 537.5, p = 0.003) and familiarity with methods for initiation of clozapine (U = 630.5, p = 0.012). As the mean ranks for both questions were higher for the pharmacy group, I can conclude that pharmacy staff were more familiar than medical staff with the NICE schizophrenia guidelines and the methods for initiation clozapine, and that this difference was statistically significant. There was no statistically significant difference between the two groups in rating of clozapine's effectiveness (U= 747.0, p = 0.201) or opinions of patient treatment satisfaction (U = 828.0, p = 0.806). Ranking of these later two questions was higher in the pharmacy group however, as shown in Table 3-4. Pharmacy staff were therefore, on average, more familiar with NICE guidance, more familiar with clozapine initiation, felt clozapine was more effective, and felt patients were more satisfied with clozapine than their medical counterparts did.

Table 3-5 Mann-Whitney test ranking for patient factor questions

Patient factor	**Professional status**	**N**	**Mean Rank**	**Asymp. Sig. (2-tailed)**
Refusal/reticence about obtaining baseline blood tests	Doctor	74	48.10	0.944
	Pharmacy staff	21	47.64	
	Total	95		
Refusal/reticence about regular blood monitoring	Doctor	75	48.99	0.731
	Pharmacy staff	21	46.74	
	Total	96		
Refusal/reticence due to need for hospital admission for titration	Doctor	62	40.66	0.166
	Pharmacy staff	15	32.13	
	Total	77		
Patient unconvinced about clozapine's efficacy	Doctor	71	46.59	0.225
	Pharmacy staff	18	38.72	
	Total	89		
Patient concerned about tolerability	Doctor	74	47.26	0.862
	Pharmacy staff	20	48.40	
	Total	94		
Significant medical factors/complications	Doctor	74	45.57	0.738
	Pharmacy staff	17	47.85	
	Total	91		

Doctors gave higher mean ranks for all questions relating to patient factors delaying clozapine initiation, as shown in Table 3-5, apart from patient concerns about tolerability, and significant medical complications, where pharmacy staff ranked higher. As explained previously, the group with higher mean ranks contained the highest scores in response to the question. Doctors therefore appeared to feel more strongly than the pharmacy staff that

patient factors (refusal of blood tests, hospital admission, concern about efficacy, tolerability or medical complications) were likely to impact on prescribing of clozapine. Despite higher mean ranks, none of these differences between the groups reached statistical significance, as shown by the Mann-Whitney test statistics presented in Table 3-5 (all non-significant at $p > 0.05$) and Table 7-37 (Appendix B).

The majority of all professionals responded that they would consider starting clozapine after two adequate antipsychotic trials (medical staff 88%, *n* = 66 of 75 respondents; pharmacy staff 74%, *n* = 17 of 23 respondents; others 61%, *n* = 22 of 36 respondents). Staff members in the 'other' professions category had a larger proportional spread towards the three and four antipsychotic trial categories than the medical and pharmacist groups, with 28% (*n* = 10 of 36 respondents) supporting starting after 3 antipsychotic trials, and 8% (*n* = 3 of 36 respondents) after 4 trials (Figure 3-14).

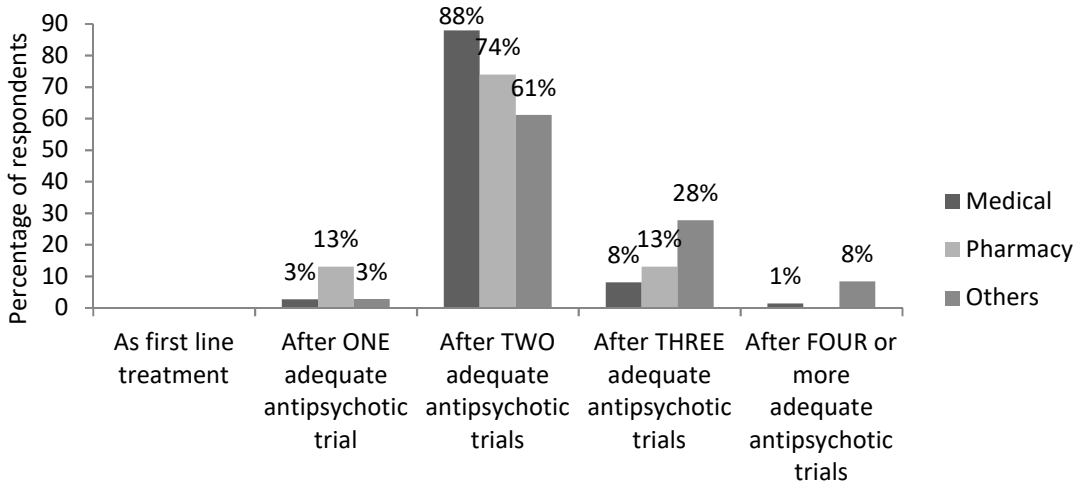

Figure 3-14 Responses to 'When would you typically consider authorising/supporting the initiation of clozapine treatment?'

When asked to estimate what proportion of patients under their care were eligible to receive clozapine but were not currently doing so, the majority of pharmacy staff (58%, *n* = 7 of 12 respondents) thought that more than a fifth of patients were in this position. A lower percentage of medical staff (47%, *n* = 25 of 53 respondents) and other professionals (38%, *n* = 10 of 27 respondents) felt that this was the case (Figure 3-15).

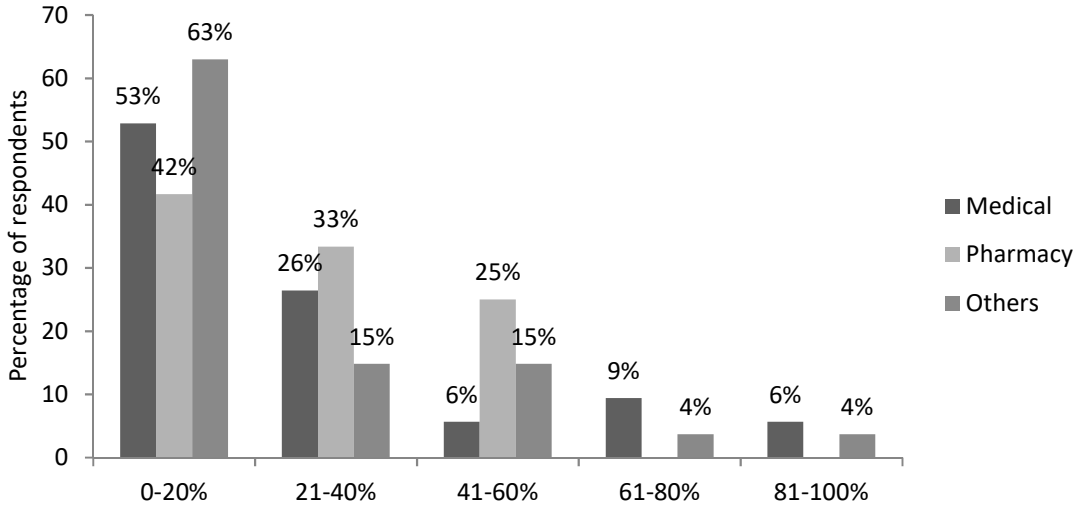

Figure 3-15 Responses to 'Approximately what percentage of patients under your care who are eligible for clozapine are not currently receiving clozapine?'

Pharmacy staff also gave differing opinions on the value of extra administrative or clinical staff in encouraging the use of clozapine – 74% (*n* = 17 of 23 respondents) thought this would be helpful, compared with 57% (*n* = 43 of 76 respondents) of doctors, and 51% (*n* = 21 of 41 respondents) of other staff members. When results from all professions were combined a narrow majority of responders (58%, *n* = 81 of 140 respondents) thought that additional clinical and/or administrative resources would facilitate the initiation of clozapine in their workplace (Figure 3-16).

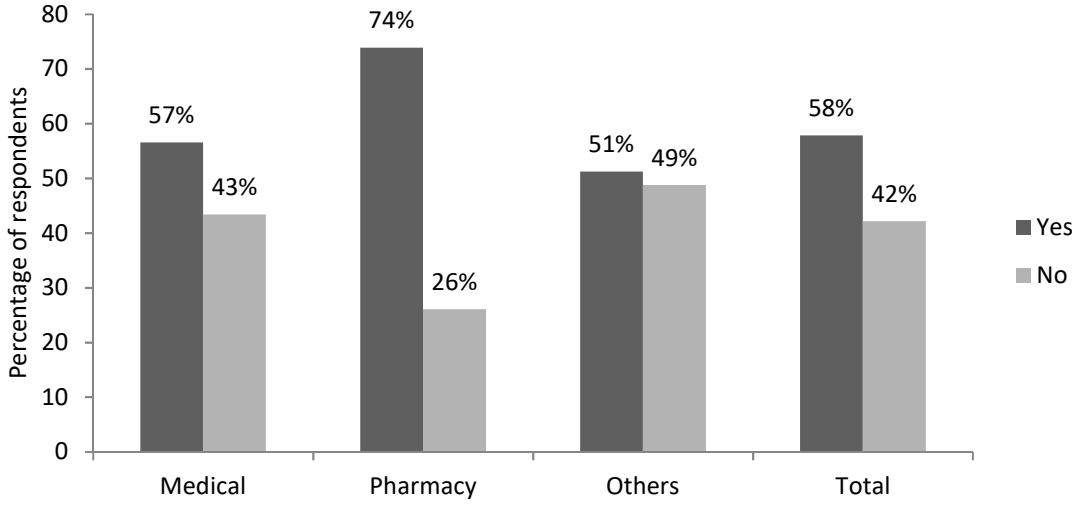

Figure 3-16 Responses to 'In your team/workplace, would additional clinical and/or administrative resources facilitate the initiation of clozapine?'

When considering staff factors in clozapine delay, mean ranking was higher for all factors in the doctor group compared to pharmacy staff, apart from administrative factors. This again

suggests doctors placing higher emphasis on the importance of these issues than pharmacy staff. However, none of these differences reach statistical significance, as shown by the test statistics in Table 3-6 ($p > 0.05$) and Table 7-38 (Appendix B).

Table 3-6 Mann-Whitney test ranking for staff factor questions

Staff factor	**Professional status**	**N**	**Mean Rank**	**Asymp. Sig. (2-tailed)**
Administrative	Doctor	69	45.10	0.751
	Pharmacy staff	21	46.81	
	Total	90		
Obtaining baseline blood tests	Doctor	69	45.42	0.762
	Pharmacy staff	20	43.55	
	Total	89		
Staff resources	Doctor	68	44.33	0.483
	Pharmacy staff	18	40.36	
	Total	86		
Need for hospital admission	Doctor	53	34.15	0.516
	Pharmacy staff	13	30.85	
	Total	66		
Cost of clozapine medication	Doctor	64	42.81	0.426
	Pharmacy staff	20	41.50	
	Total	84		
Concerns about tolerability	Doctor	69	46.86	0.080
	Pharmacy staff	19	35.95	
	Total	88		
Significant medical factors/compliance	Doctor	69	45.10	0.942
	Pharmacy staff	20	44.65	
	Total	89		

Table 3-7 shows that mean ranking of enabling factors for clozapine initiation was higher for all suggestions in the doctor group, apart from the availability of dedicated hospital beds, where pharmacy staff ranked this higher. The differences between the groups did not reach statistical significance for any of the enabling factors (see also Table 7-39, Appendix B).

Table 3-7 Mann-Whitney test ranking enabling factor questions

Enabling factor	Professional status	N	Mean Rank	Asymp. Sig. (2-tailed)
Additional administrative support	Doctor	68	46.15	0.117
	Pharmacy staff	19	36.32	
	Total	87		
Additional staff dedicated to obtaining baseline blood tests	Doctor	69	46.55	0.275
	Pharmacy staff	20	39.65	
	Total	89		
Dedicated hospital beds to enable initiation of clozapine as an inpatient	Doctor	62	37.04	0.388
	Pharmacy staff	13	42.58	
	Total	75		
Dedicated staff to arrange and monitor the initiation of clozapine as an outpatient	Doctor	66	42.11	0.934
	Pharmacy staff	17	41.59	
	Total	83		
Dedicated day-hospital placements to initiate clozapine as an outpatient	Doctor	63	41.06	0.967
	Pharmacy staff	18	40.81	
	Total	81		

In summary, pharmacy staff reported themselves more familiar with NICE guidelines (median = 'very familiar') than doctors (median = 'fairly familiar', $p = 0.003$). Pharmacy staff also felt more familiar with methods of initiation of clozapine (median = 'very familiar') than doctors (median = 'fairly familiar, $p = 0.012$). Differences in responses to other questions did not reach statistical significance.

3.4 Summary

In total, 144 clinical staff completed the questionnaire. The majority (81%) of respondents were 'fairly' or 'very' familiar with clozapine prescribing guidelines. Members of pharmacy staff rated themselves more familiar with the guidelines and also procedures for initiation of clozapine than medical staff. Barriers to prescribing most commonly stated as being 'very frequently' a problem were patient concerns about tolerability of clozapine or patient refusal to adhere to blood test monitoring. Staff members also felt medical complications frequently prevented clozapine prescription. Dedicated staff or day hospital placements devoted to clozapine initiation were identified as factors most likely to increase prescribing of clozapine. Professionals identified the dominant barriers to prescribing as being patient focussed – refusal of blood test monitoring or concerns about tolerability. Clinician fears about compliance or medical complications were also important. The development of outpatient

services specifically tasked with initiating clozapine may help to increase the frequency of prescribing of clozapine earlier in treatment than is currently seen.

3.5 Publications arising from this study

See Appendix I: **Siobhan Gee**, Francis Vergunst, Oliver Howes, David Taylor (2014) Practitioner attitudes to clozapine initiation. *Acta Psychiatrica Scandinavica*, 130(1):16

4 Patient attitudes to clozapine initiation

4.1 Introduction

Despite the established unique efficacy of clozapine in treatment-resistant schizophrenia, as shown in chapter 2 it remains under-prescribed (148). The reasons for this are not clear but perhaps are most likely to lie at the interface between the patient and prescriber. I have shown in chapter 3 that the barriers psychiatry practitioners cited as most frequently preventing clozapine prescription are: patient refusal of regular blood testing; patient refusal of baseline blood testing; patient concerns about tolerability; medical complications; patient refusal of hospital admission; and the patient being unsure of efficacy (149). If one excludes co-morbid medical complications, the top five reasons that practitioners report for not prescribing clozapine are patient-related. This is at odds with research examining patient opinions of clozapine which are overwhelming positive, with tolerability and the need for blood tests considered to be problems far less frequently by patients than by clinicians (150). However, there is a significant bias in that the rather limited available literature is confined to the opinions of patients who are *already* taking clozapine. By definition this cohort of patients will have consented to treatment and remained compliant with it. Surveys of existing patients could be said to confirm only what might otherwise be assumed. Therefore, in this study I surveyed the perhaps more relevant views of those patients who are eligible for, but are not currently prescribed, clozapine, aiming to better understand the patient-related barriers to clozapine initiation.

4.1.1 Objectives

- To establish the familiarity and acceptability of clozapine to patients who have never received clozapine, but would be eligible to do so.
- To elucidate factors that put patients off trying clozapine.

4.2 Method

In order to inform the questions to be asked in the survey, conducting a focus group of patients was considered. This would however be difficult to run with a group of patients all suffering acute psychosis, and additionally the key purpose of this study was to examine whether the opinions of clinicians expressed in the previous survey were borne out when presented to patients, rather than to develop new themes of enquiry. Instead, the questionnaire for use in the study was designed to provide complementary answers to the questionnaire previously administered to psychiatric clinicians. It was drafted, commented on and adjusted by the research team. Alterations were made to the clarity of questions asked and simplicity of possible answers. It was then piloted to 5 patients, and no further changes were required. The questionnaire is available in Appendix E.

Over a 593 day period, patients admitted to the acute wards at the Bethlem Royal Hospital were assessed for eligibility for the study. Eligibility for inclusion in the study was determined by review of clinical case notes against the following criteria:

- Admission to an acute psychiatric ward at the Bethlem Royal Hospital
- Prescription of two or more antipsychotics over the course of the illness (up to and including the current prescription), each for at least 6 weeks and at a minimal effective dose (defined as outlined in chapter 2)
- Diagnosis of schizophrenia or schizoaffective disorder
- No previous trials of clozapine

It was assumed that the principal reason for admission was psychiatric relapse, and that this could be due to medication failure. Assessment of compliance with medication prior to admission was not made. Detailed assessment of physical health pertinent to the safety of clozapine initiation was not made, but where it was immediately obvious from the clinical notes that patients would be excluded for these reasons from clozapine challenge, these patients were marked as ‘non-participants’.

Likert scales were used where possible, rather than the multiple choice style used in the practitioner survey. Oral multiple choice questions would have been lengthy to explain to participants, and also would have increased the risk of interviewer bias as they attempt to fit any answer given into the predetermined response options. I offered 'don't know' where possible to reduce the chance of yea saying (151), and used follow-up open-ended questions to try to fully elicit participants' understanding. Open-ended questions can produce low response rates, and are also open to the potential for the researcher imposing their own interpretation on the answers, especially where participants are less articulate (151), and so open-ended questions were linked as much as possible to Likert or yes/no questions.

Patients were approached for inclusion in the survey by the lead investigator (SG), and if consent was given then a face-to-face questionnaire administered (also by SG). Patients were first asked whether or not they had heard of clozapine. If they answered "no" then a brief paragraph (see 0) detailing the indication for clozapine (an antipsychotic, used to treat the symptoms of schizophrenia described as a reduction in hallucinations, improvement in concentration and thinking), common side effects (constipation, drowsiness, hypersalivation, dizziness on standing, tachycardia) and rare side effects (a reduction in white blood cells) was read to them. They were fully informed of the need for blood testing and its frequency, and also that some people found clozapine to be the only medication effective for them. This paragraph was also read to patients who replied that they had already heard of clozapine, if it became clear later in the interview that there were aspects of the treatment that they were either not aware of, or did not understand fully. It was not initially read to all patients as I felt that this was likely to reduce participation in the study given the effect of active psychosis on the ability of patients to concentrate for long periods.

Participants were then asked whether they had ever been asked to take clozapine, and if so what the outcome was. They were asked whether they would consider taking clozapine now, were it to be offered to them. A follow-up opened-ended question was asked to explore why they would/wouldn't consider taking clozapine now.

Likert scales were used to assess patients' opinions on the need for baseline blood tests, regular blood tests, the side effects, and the potential need for hospital admission to initiate clozapine. Written descriptions were used to present the possible options, which ranged from '0' (that doesn't bother/worry me at all), '1' (I'd be slightly bothered/worried but I'd still be willing to try it), '2' (I'd be fairly bothered/worried but I'd still be willing to try it), '3' (I'd be very bothered/worried but I'd still be willing to try it) to '4' (I wouldn't try clozapine because of this/the side effects). Participants were also asked whether starting clozapine at home would be preferable to being admitted to hospital in order to titrate the dose.

Finally, participants were asked to compare, as far as they were able, clozapine with medicines they had taken in the past, or were taking currently, and to rate how much they thought clozapine would help them. A Likert scale was again used to gather responses, ranging from '0' (clozapine would be a lot less helpful than other medicines I've had), '1' (clozapine would be slightly less helpful than other medicines I've had), '2' (clozapine would be about the same as other medicines I've had), '3' (clozapine would be a bit better than other medicines I've had), to '4' (clozapine would be a lot better than other medicines I've had'). Where possible, their reasons for their answers were also noted.

Patients who fully or partially completed the questionnaire were designated 'participants', and patients who refused to take part, or could not be interviewed for other reasons were designated 'non-participants'.

4.2.1 Statistical analysis

Independent *t*-tests for continuous variables and Pearson's chi-squared test for categorical variables were used to compare the demographics of patients in the participating and non-participating groups. All data were analysed using SPSS version 22.

4.3 Results

In total, 468 patients admitted to the wards were assessed for entry into the study. Of these, 116 fulfilled the eligibility criteria for the study and of these 25% (29 of 116 patients) refused

to take part, 5% (6 of 116 patients) were considered too unwell to provide informed consent, 10% (12 of 116 patients) were discharged before an interview could take place, and 7% (8 of 116 patients) were excluded for other reasons (predominantly a lack of sufficient English or transfer to another hospital before interview) (Table 4-1). The remaining 61 patients were considered 'participants' in the survey, and of these 82% (50 of 61 patients) answered all the questions asked, with a further 18% (11 of 61 patients) answering at least 1 question.

Table 4-1 Demographics and participation details shows the demographics of the total cohort, participants, and non-participants. The majority of the total group (72%), participants (79%) and non-participants (66%) were male. The majority in each group were also black (total group = 53%, participants = 51%, non-participants = 56%) and were diagnosed with schizophrenia (total group = 76%, participants = 74%, non-participants = 78%). There were no statistically significant differences between the demographics of the participant and non-participant groups.

Table 4-1 Demographics and participation details

		Total cohort, *N* = 116	**Participants, *n* = 61**	**Non-participants, *n* = 55**	***p***
Mean age, years (range)		43 (19 - 76)	42 (20 – 71)	44 (19 – 76)	0.31
Gender, male (%)		84 (72)	48 (79)	36 (66)	0.05
Ethnicity, *n* (%)	White	31 (27)	18 (30)	13 (24)	0.08
	Black	62 (53)	31 (51)	31 (56)	
	Asian	12 (10)	4 (7)	8 (15)	
	Mixed or other	11 (9)	8 (13)	3 (5)	
Mean days between admission and interview (range)		13 (0 – 68)	11 (0 – 61)	15 (1 – 68)	0.21
Diagnosis, *n* (%)	Schizophrenia	88 (76)	45 (74)	43 (78)	0.15
	Schizoaffective disorder	28 (24)	16 (26)	12 (22)	

Just over half of the patients surveyed had heard of clozapine (54%, 33 of 61 patients), and a fifth (19%, 11 of 57 patients) recalled being asked to consider taking it as a treatment for their illness (Table 4-2).

Table 4-2 Responses to 'Have you heard of a medication called clozapine?'

	N	**Yes, *n* (%)**	**No, *n* (%)**	**Don't know, *n* (%)**
Have you heard of clozapine?	61	33 (54)	26 (43)	2 (3)
Have you ever been asked to take clozapine?	57	11 (19)	40 (70)	6 (11)

When asked for their probable response if asked to take clozapine now, 35% of patients said they would refuse it (20 of 57 patients) although this was a narrow majority, with 30% (17 of 57 patients) saying that they would be willing to try it (Table 4-3).

Table 4-3 Responses to 'If you were asked to take clozapine now, how would you respond?'

		***N* (%)**
If you were asked to take clozapine now, how would you respond?	I'd take it	17 (30)
	I wouldn't take it	20 (35)
	I might take it	2 (4)
	Don't know	7 (12)
	Other	1 (2)

Of those seventeen subjects that said they would take clozapine if it were offered to them now, fourteen provided further explanation (see Appendix F). The most frequent theme (5 patients) that emerged was that the patient wanted their mental health to improve, and felt that clozapine would be helpful in this way:

> "I want my mental health to recover"

> "I need something in addition to my current medicines"

The next most common statements (4 patients) were related to trust in the opinion of the professionals caring for them:

> "If it would help I'd take it. I trust the doctor's opinion – if they say I need it then I'll take it"

> "I know it would do me good. I trust you."

For patients who stated that they would not take clozapine, might take it or were not sure if they would take it if it were offered to them, 38 provided a more detailed response. The most commonly cited reason (15 patients) for either refusing clozapine or being unsure about treatment was related to the side effects or blood monitoring, and of these most responses

focussed on the effects on the white blood cells or the blood monitoring in some way (8 patients):

> "There are more negatives than positives… the side effects"
>
> "The constant monitoring. The side effects – salivation, drowsiness. I don't like needles."
>
> "It kills white blood cells"
>
> "The white cell thing sounds risky"

Other common themes included not believing that any medication was necessary at the moment (5 patients), being happy with the current medication (4 patients) and being unsure what the effects of clozapine might be (3 patients).

Table 4-4 Responses to Likert scale-measured questions

		That doesn't bother/worry me at all	**I'd be slightly bothered/worried but would still try clozapine**	**I'd be fairly bothered/worried but would still try clozapine**	**I'd be very bothered/worried but would still try clozapine**	**I wouldn't try clozapine because of this**	**Don't know**	**Other**
	N	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
How would you feel about having blood taken before starting clozapine?	54	19 (35)	6 (11)	5 (9)	5 (9)	17 (32)	1 (2)	1 (2)
How would you feel about having blood taken regularly whilst taking clozapine?	54	15 (28)	5 (9)	4 (7)	7 (13)	22 (41)	0 (0)	1 (2)
How much do the side effects of clozapine worry you?	53	9 (17)	8 (15)	1 (2)	10 (19)	23 (43)	2 (4)	0 (0)
How would you feel about being admitted to hospital in order to start clozapine?	51	15 (29)	0 (0)	7 (14)	3 (6)	25 (49)	0 (0)	1 (1)

When asked how they felt about having blood taken before starting clozapine, a narrow majority of participants (35%, 19 of 54 patients) reported that this wouldn't bother them at all (Table 4-4). The opposite answer, 'I wouldn't try clozapine because of this' was the next most common response (32%, 17 of 54 patients). Proportionally more patients reported that regular blood tests would put them off trying clozapine (41%, 22 of 54 patients), with 28% (15 of 54 patients) stating that this wouldn't bother them at all. The side effects of clozapine were a barrier to clozapine for a substantial proportion of patients, with 43% (23 of 53 patients) saying that this would put them off clozapine entirely and 19% (10 of 53 patients) reporting that the side effects would worry them very much. In contrast, 17% (9 of 53 patients) said the side effects didn't worry them at all, and 15% (8 of 53 patients) said they would be slightly worried. When asked how they would feel about coming into hospital in order to initiate clozapine, the largest proportion of patients (49%, 25 of 51 patients) said this would put them off trying clozapine. However, a significant proportion (29%, 15 of 51 patients) reported that being admitted in order to start clozapine wouldn't bother them at all.

When asked which side effects particularly worried them, 34 patients gave more detailed answers. Of these, the most common side effect cited was dizziness or any cardiac complication (8 patients), followed by the effects on white blood cells (6 patients). Some patients expressed beliefs they held about the medicine both in general and in relation to side effects:

> "I see other patients that drool, it means you are disabled."

> "The strength of the pill makes me worried about collapsing. You can't miss a day of taking clozapine, so you are basically dependent on it."

Others weighed the balance of side effects against the potential benefits:

> "Medicines are there to improve and stay positive so I'm not worried about side effects."

> "I know other people who take clozapine. For them the psychosis is so bad the side effects are worth taking. It's a balance for each individual. Therefore if I needed clozapine I wouldn't care about the side effects because I would need it."

> "I've had drooling on amisulpride before, so I wouldn't want this to happen again. I don't need clozapine. But I recognise that if psychosis is really bad then people need clozapine and then for them any negative problems (having to have bloods done, the side effects, being admitted)

> are outweighed by the benefits. So the problem is people not having any insight into the severity of their psychosis."

A clear majority of participants (67%, 34 of 51 patients) felt that starting clozapine at home would be better than being admitted to hospital, although a significant proportion (26%, 13 of 51 patients) disagreed (4 (8%) did not give an opinion).

Comments made by patients who stated that they would rather come into hospital to start a medicine than be at home included:

> "I would be worried about starting clozapine at home because side effects wouldn't be monitored."

> "A professional should be starting medicines so it is better to be in hospital for this, not at home."

> "If you feel ill it's better to come into hospital for medicines to be started because that's where the doctors are – it's better to be with them."

When asked to compare the likely effect of clozapine to other medicines they had taken, the majority of patients (32%, 16 of 50 patients) felt that it would be "a lot less helpful" for them, 3 (6%) felt it would be slightly less helpful, and 6 (12%) felt it would be "about the same". Twelve participants (24%) thought clozapine would be more helpful to them than their previous medication; "a bit better" (7 of 50 patients, 14%) or "a lot better" (5 of 50 patients, 10%). The second most common answer was "I don't know" (20%, 10 of 50 patients). Three participants' answers could not be classified.

4.4 Summary

I interviewed 61 of 116 eligible patients and 50 (82%) answered all questions. At interview, 33 of 61 participants (54%) had heard of clozapine and 17 of 57 (30%) said they would take it if asked. Overall, 31 of 54 (57%) respondents said blood testing would not preclude them taking clozapine. The necessity for hospital admission was seen as the greatest barrier to receiving clozapine – 25 of 51 respondents (49%) stated this would be a reason for refusing clozapine. Concerns about adverse effects of clozapine were considered sufficient to refuse clozapine in 23 of 53 (43%) respondents. Overall, 12 of 50 (24%) respondents felt clozapine would be helpful to them. Patients' acceptance of clozapine is likely to be improved by

offering the opportunity to start clozapine at home and by improved education about the therapeutic benefits of clozapine and the management of its adverse effects. Blood testing does not appear to be an important barrier to initiation of clozapine.

4.5 Publications arising from this study

See Appendix I: **Siobhan Gee**, Sukhwinder Shergill, David Taylor (2017) Patient attitudes to clozapine initiation. *International Clinical Psychopharmacology*, 32(6):337-3

5 Factors associated with changes in hospitalisation in patients prescribed clozapine

5.1 Introduction

There is now a large body of evidence demonstrating that long periods of untreated psychosis are associated with increased symptom severity, and that the longer this delay is, the worse the symptoms are (152). Clarke et al. (153) showed that the long term consequences of a prolonged untreated psychosis include a reduced likelihood of remission and reduced functional outcome, as well as increased psychopathology. Cognitive function (154-157), occupational functioning (158, 159), forensic risk (160), subsequent psychiatric admissions (161), and even smoking habits (162) have all been shown to be adversely affected by a long untreated psychosis. The initiation of antipsychotic medication in the first episode of psychosis results in better outcomes (163-166), and the latency of that treatment is a significant predictor of time to treatment response (167). Further than this, a long untreated psychosis is also associated with poorer response to antipsychotic treatment once it is initiated (168).

It is clear that the duration of untreated psychosis in first episode schizophrenia affects eventual response (both in latency and magnitude) to antipsychotics. It is not clear if delays in starting clozapine treatment with consequent periods of poorly or incompletely treated psychosis also result in an adverse effect on response to clozapine and on clinical and functional outcomes. This study aims to examine the relationship between the delay in receiving clozapine and treatment outcomes after clozapine is started using inpatient admissions as a proxy marker for relapse, and investigate the consequence of stopping clozapine.

5.1.1 Objectives

- To investigate the effect of clozapine on inpatient bed use.

- To examine whether the theoretical delay to starting clozapine affects inpatient bed use, once clozapine has been started.
- To establish whether a patient's age, ethnicity, diagnosis, gender, number of previous non-clozapine antipsychotics or whether they continued or discontinued clozapine affects inpatient bed use, once clozapine has been started.

5.2 Method

I used the same patient data set described in chapter 2 for this study, with admissions data gathered from the time of diagnosis up to the study end date (01.11.14).

5.2.1 Exclusion criteria

Of the original data set of 149 patients, 47 were excluded from this study (Table 5-1). Of these 47, 31 patients had had contact at some point during their treatment history with forensic services. Forensic psychiatric services are those that specialise in the assessment and treatment of people with mental health disorders undergoing legal or court proceedings, or who have offended (169). For these patients, factors other than their mental state are likely to influence their length of stay in psychiatric services, as the Ministry of Justice may control their discharge date.

Between the end of the previous study period and the end of the current study period 5 patients died, and these were also excluded from the study. Patients who were discharged out of SLaM were lost to follow up as their subsequent clinical notes were inaccessible. This accounted for 9 patients. Of the remaining 2 excluded patients, 1 was found to be a duplicate, and 1 had received clozapine before the start date of the previous study.

Table 5-1 Demographic details for patients excluded from analysis

		Forensic patients (*n* = 31)	**Deaths (*n* = 5)**	**Lost to follow up (*n* = 9)**	**Excluded (*n* = 2)**
Male, *n* (%)		29 (94)	4 (80)	6 (67)	0 (0)
Age at first clozapine prescription, mean years		30.32	38	24.67	38.5
Ethnicity, *n* (%)	White	10 (32)	3 (60)	5 (56)	2 (100)
	Black	18 (58)	2 (40)	4 (44)	0 (0)
	Asian	0 (0)	0 (0)	0 (0)	0 (0)
	Mixed	3 (10)	0 (0)	0 (0)	0 (0)
	Other	0 (0)	0 (0)	0 (0)	0 (0)
Diagnosis, *n* (%)	Schizophrenia	23 (74)	4 (80)	7 (78)	1 (50)
	Schizoaffective	3 (10)	0 (0)	1 (11)	0 (0)
	Other	5 (16)	1 (20)	1 (11)	1 (50)

5.2.2 Inclusion criteria

Demographics and pre-clozapine prescribing histories were available as described previously from the data set (see chapter 2). Data on inpatient admissions were also gathered from the clinical notes. These data were collected from the date of first presentation of the patient to mental health services to the end date of the study (01.11.14). The data collected were:

- Number of admissions
- Length of admission
- Reason for admission (where clearly stated)

All inpatient admissions to psychiatric services were considered an 'admission', regardless of the country in which the admission took place, or of the type of psychiatric institution to which the patient was admitted. Inpatient admissions to institutions other than those specifically designated as 'psychiatric' were excluded (e.g. Admissions to general medical hospitals), even if the patient was reviewed by a psychiatrist during this admission, as the primary reason for admission was assumed to something other than a psychiatric relapse. If the patient was subsequently transferred from a medical (or other) facility to a psychiatric inpatient institution, then the latter period was considered an 'admission' in the context of this study, and the start date of admission taken as the date of transfer to psychiatric services.

5.2.3 Designation of index admission

The ‘index admission’ was defined as the admission during which clozapine was commenced, if clozapine was commenced whilst the patient was an inpatient. Acknowledging the different methods for data analysis used by other authors (see discussion, chapter 7), I performed sensitivity analyses for 5 different methods (Figure 5-1):

1. Simple mirror image division (30, 170-178) – days of admission before clozapine are attributed to the pre-clozapine period, days of admission after clozapine are attributed to the post-clozapine period.
2. Excluding the entire index admission (84, 90, 177, 179, 180)
3. Attributing the index admission up to the point of clozapine initiation to the pre-clozapine period, excluding the first 14 days of the post-clozapine period from analysis, and then attributing any remaining days in the index admission to the post-clozapine period (177, 181)
4. Attributing the index admission pre-clozapine and the first 14 days of clozapine treatment to the pre-clozapine period, then attributing any remaining days of the index admission to the post-clozapine period (177)
5. Attributing the index admission up to the point of clozapine initiation to the pre-clozapine period, then excluding any remaining days of the index admission from analysis (179)

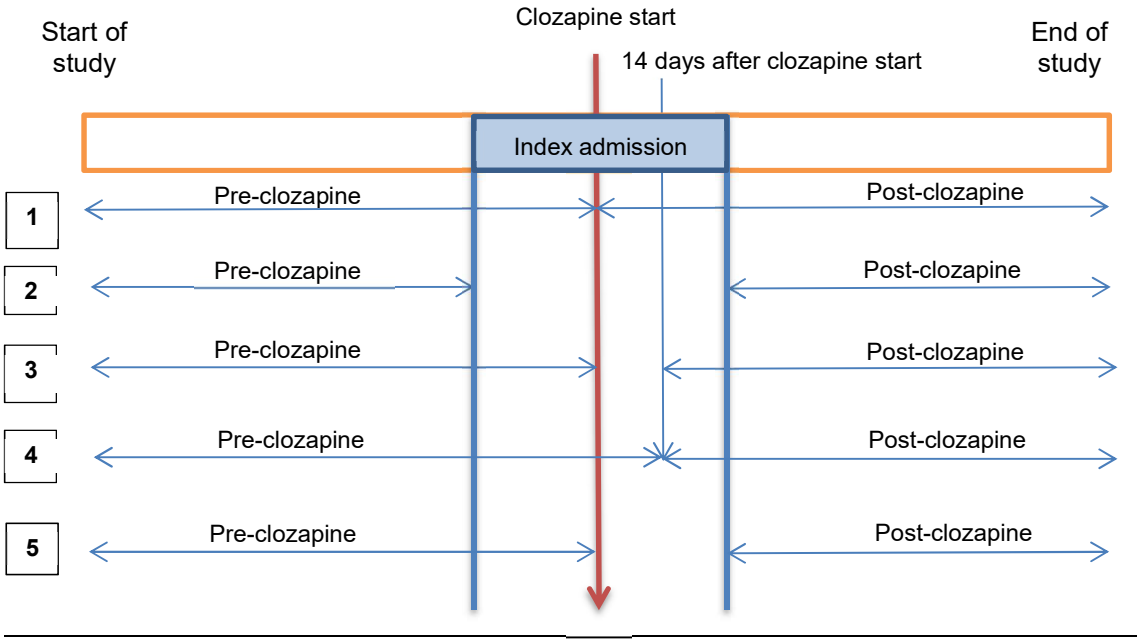

Figure 5-1 Sensitivity analysis methods

I analysed the data using an intent to treat method, and separately for clozapine continuers and discontinuers.

5.2.4 Clozapine discontinuation data

Clinical notes were used to gather data for:

- Date clozapine was stopped
- Date clozapine was restarted
- Medication switched to once clozapine was stopped
- Reason for clozapine being stopped

Clozapine was considered to be 'stopped' where the stop was followed by a deliberate switch to a different antipsychotic medication. Periods of non-compliance with clozapine, followed by retitration directly onto clozapine were not considered as a 'stop' episode, even if the retitration included a period of prescribing of a second antipsychotic to 'cover' the clozapine dose escalation. Short term uses of other medication pending retitration were also excluded, where it was clear that the intention of the prescriber was to retitrate, and the delay was caused only by practical or logistic factors (re-registration of the patient with the clozapine

monitoring company, obtaining medication, or organising phlebotomy), and not by a clinical decision not to restart. Further discussion and analysis of these data are presented in chapter 6.

5.2.5 Ethnicity categories

Ethnicity codes were gathered directly from clinical notes. Where required for statistical analysis, ethnicity categories were created using the standardised categories defined by the Office for National Statistics (ONS) census (182). Thus, the categories were as outlined in Table 5-2.

Table 5-2 Ethnicity code categories

Ethnicity category (ONS Census)	Self-identified ethnicity code
White	British Irish English Turkish Cypriot Portuguese Polish Other white
Black	African Caribbean Black British Eritrean Nigerian Ghanaian Mixed Black Other African Other Black
Asian	Bangladeshi Indian Pakistani Chinese British Asian Mixed Asian Sri Lankan Tamil Other Asian
Mixed	White and Black African White and Black Caribbean White and Asian Caribbean and Asian Any other mixed background
Other	Arab Iranian Kurdish Other

5.2.6 Statistical analysis

For the intent to treat population (all patients, regardless of stopping or continuing clozapine), bias was tested using scatter plots, *z*-scores, skew and kurtosis, and tests of normality (Kolmogorov-Smirnov and Shapiro-Wilk). *z*-scores and normality tests have been described in detail in Chapter 2. There are two ways in which a population can deviate from normal – skew, which is a lack of symmetry around the mean, and kurtosis, which is how much the scores within the data cluster around the ends of the distribution curve. Positively skewed patterns have the most frequent scores clustered at the lower end of the scale, and negatively skewed patterns have the most frequent scores clustered at the opposite, higher end of the

scale. Data sets with positive kurtosis have many scores in the tails of the distribution (also termed 'heavy-tailed' or leptokurtic). Data sets with negative kurtosis have fewer scores in the tails (also termed 'light-tailed' or platykurtic). In a perfectly normal distribution, the values of skew and kurtosis are 0. Any values above or below this indicate a deviation of the data from normal.

Splitting the data into clozapine continuers and discontinuers, bias was examined using Q-Q plots, and paired samples *t*-tests and Wilcoxon signed rank tests used to compare days of admission and numbers of admissions before and after clozapine initiation.

Paired samples *t*-tests were used to compare data before and after clozapine initiation. The *t*-test is carried out by comparing the sample means for each set of data (in this case, data for before and after clozapine). If the samples come from the same population, the means are expected to be roughly equal. As the *t*-test uses numerical sample means, it can only be applied to continuous variables (in this data set, both variables are continuous). The paired samples test is appropriate here (rather than the independent samples *t*-test) as each patient is a member of both groups (before and after clozapine).

Wilcoxon signed rank test examines differences between results in two groups, where the results from each group come from the same participants (in this case, patients were in the 'pre-clozapine' and 'post-clozapine' groups). It is the non-parametric equivalent of the paired samples *t*-test presented above. Wilcoxon signed rank test is particularly appropriate for this set of data as it compares the results in each group by ranking the scores, but also assigns the sign (positive or negative) of the difference in the scores to the rank. In this way it examines the change in scores between the two groups. For this analysis, the difference in days of admission was calculated by taking the days post-clozapine away from the days pre-clozapine, and so a negative score means a higher number of days spent in hospital after clozapine was started. A difference of 0 means that there was no difference in hospital bed days before or after clozapine.

Linear regression (ANOVA) was used to investigate whether the length of clozapine delay affected admission data before and after clozapine was started. Multivariate analysis of variance (MANOVA) was used to look at the effect of the number of pre-clozapine antipsychotics, age, gender, ethnicity, diagnosis and continuing or discontinuing clozapine on admission data. Assumptions were tested using Box's test of equality of variance matrices, and multivariate and univariate tests carried out. The MANOVA was followed up with discriminant function analysis where appropriate, and also conducted separately for clozapine continuers and discontinuers. Data were analysed using IBM SPSS Statistics 22.

5.3 Results

5.3.1 Intent to treat group

The majority of patients were male (62.7%), with a mean age of 38 years (Table 5-3). The most commonly represented ethnic group was British (38.2%), followed by Black African (11.8%) and Black British (8.8%). Most patients had a diagnosis of schizophrenia (66.7%).

Table 5-3 Group demographics

		Intent to treat group, *n* (%)	Continuers, *n* (%)	Discontinuers, *n* (%)
N		102	67	35
Male		64 (62.7)	37 (55.2)	27 (77.1)
Mean age, years		38.64	39.43	37.11
Ethnicity	White	4 (3.9)	3 (4.5)	1 (2.9)
	Black British	9 (8.8)	4 (6.0)	5 (14.3)
	Black African	12 (11.8)	10 (14.9)	2 (5.7)
	Caribbean	8 (7.8)	4 (6.0)	4 (11.4)
	British	39 (38.2)	27 (40.3)	12 (34.3)
	Chinese	2 (2.0)	0 (0)	2 (5.7)
	Iranian	1 (1.0)	1 (1.5)	0 (0)
	Other African	7 (6.9)	5 (7.5)	2 (5.7)
	Eritrean	2 (2.0)	1 (1.0)	1 (2.9)
	Arab	1 (1.0)	0 (0)	1 (2.9)
	Black and white Caribbean	7 (6.9)	6 (9.0)	1 (2.9)
	Cypriot	1 (1.0)	0 (0)	1 (2.9)
	Indian	3 (2.9)	2 (3.0)	1 (2.9)
	Pakistani	2 (2.0)	2 (3.0)	0 (0)
	Turkish	1 (1.0)	0 (0)	1 (2.9)
	Sri Lankan	1 (1.0)	0 (0)	1 (2.9)
	Bangladeshi	1 (1.0)	1 (1.5)	0 (0)
	Other	1 (1.0)	1 (1.5)	0 (0)
Diagnosis	F20	68 (66.7)	43 (64.2)	25 (71.4)
	F25	17 (16.7)	12 (17.9)	5 (14.3)
	F31	6 (5.9)	6 (9.0)	0 (0)
	Other	11 (10.8)	6 (9.0)	5 (14.3)

5.3.1.1 Method 1

This is a simple mirror image division method – days of admission before clozapine initiation are attributed to the pre-clozapine period, days of admission after clozapine initiation are attributed to the post-clozapine period.

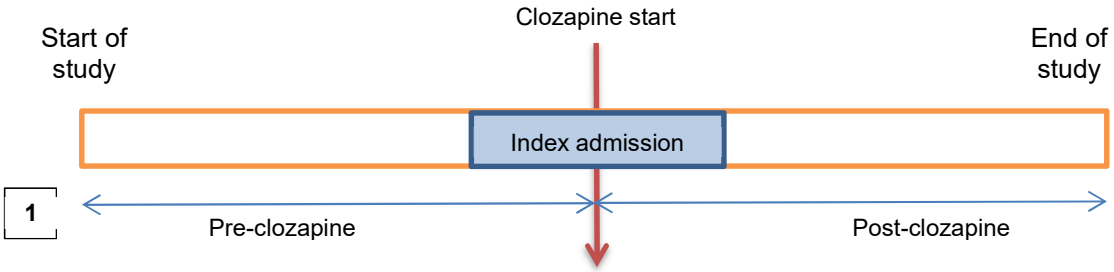

Figure 5-2 Method 1 analysis

Outcome data are presented in Table 5-4. Overall, an increase in the number of days of admission after clozapine was started was found, but the number of admissions per year decreased.

Table 5-4 Outcome data, intent to treat group, analysis method 1

		Bias			
		Kolmogorov-Smirnov		**Shapiro-Wilk**	
		$D_{(102)}$	***p***	**$W_{(102)}$**	***p***
Mean number of days of admission per year pre-clozapine	66.70				
Mean number of days of admission per year post-clozapine	69.69				
Mean number of admissions per year pre-clozapine	0.95				
Mean number of admissions per year post-clozapine	0.21				
Net change in days of admission pre-post clozapine per year[a]	-2.98	0.213	< 0.0005	0.871	< 0.0005
Net change in number of admissions pre/post clozapine per year[a]	0.73	0.200	< 0.0005	0.720	< 0.0005
Mean theoretical clozapine delay (years)	3.93	0.213	< 0.0005	0.791	< 0.0005

[a]negative number denotes higher number of days/admissions post-clozapine

5.3.1.1.1 Bias

As discussed previously in chapter 2, possible sources of bias in the data are outlying data scores, and violations of assumptions (normality and homoscedasticity or homogeneity of variance). The scatterplot for these data is presented in Appendix G (Figure 7-3), and shows some outlying data points at both extremes of the primary outcome. On examination, these outliers occur due to the entire mirror image study period being entirely within one single admission, meaning that these patients are always inpatients (100% of the time spent both pre- and post-clozapine is as an inpatient). This introduces bias to the data set, as the reality for these patients is that much less than 100% of their total history is spent as an inpatient. This situation affects two cases. For two further cases either the pre- or the post-clozapine

periods are entirely within one single admission. This bias will affect the estimate of the mean, the sum of the squared error and the standard deviation. These data cannot be trimmed from the data set as they are from the inclusion population.

Also as described in chapter 2, *z*-scores can be used to find outliers. The frequencies of these scores in this data set are shown in Appendix G (Table 7-48). For this data set, 1% of the cases were above 3.29 (extreme cases), 3.9% were greater than 2.58 (more than the expected 1% for probable outliers), and 2.9% had values greater than 1.96 (potential outliers). The remaining cases constitute 92.2% of the values, and these lie within the normal range. Therefore the data are not consistent with what would be expected from a normal distribution, where 95% of the data would be expected to fall with the normal range.

The values for the skewness and kurtosis of these data are presented in Appendix G (Table 7-49). For the net change in the number of admissions per year, the clozapine theoretical delay, and the total number of antipsychotics prescriptions used before clozapine, the skew is positive, indicating a concentration of data points on the left side of the distribution curve. For net change in days of admissions per year, the skew is negative but very close to zero. All the measures show positive kurtosis, with the net change in number of admissions per year being the most affected. This indicates a heavy and pointy tailed distribution. All the values for *z*-skewness and *z*-kurtosis are above 3.29, meaning that they are significant at $p < 0.001$, indicating a problem with both skew and kurtosis in the data.

As the z-scores showed a problem with outlying data scores in this sample, I performed tests for normality. The results from these tests are presented in detail in Appendix G (Table 7-50), and above in Table 5-4. From the Kolmogorov-Smirnov and Shapiro-Wilk tests, scores for the net change in days of admission per year, the net change in the number of admissions per year, the total number of antipsychotic prescriptions before clozapine, and the theoretical delay to starting clozapine, are significantly non-normal ($p < 0.0005$).

5.3.1.1.2 Wilcoxon signed rank test

As the data are not normally distributed, as shown by the tests above, I used the non-parametric Wilcoxon signed-rank test to establish differences in the change in days of admission per year pre- and post-clozapine. The result for this test is shown in Appendix G (Figure 7-4).

The histogram shows positively ranked results (those where there were a higher number of days spent in hospital before clozapine was started) in brown, and negatively ranked results in blue. For these data there were 55 positive ranks, 40 negative ranks and 7 ties (where the number of days of admission was the same before and after clozapine). The test score, *T*, is the sum of the positive ranks and is 2574.500. The standard error for this result is 269.407, and the *z*-score, which is calculated from the *T* score, is 1.093 (denoted as the 'standardized test statistic' in the output table). This *z*-score is non-significant at $p = 0.274$. This therefore finds no significant difference in the number of days spent in hospital after clozapine was initiated.

I then repeated the test for the number of admissions per year before and after clozapine was started – again, the difference in admissions was calculated by taking the number of admissions per year post-clozapine away from the number of admissions per year pre-clozapine, and so a negative number denotes a larger number of admissions after clozapine had started. The results for this test are shown in Appendix G (Figure 7-5).

For these data there were 81 positive ranks, 10 negative ranks and 11 ties. The test score, *T*, is 3841. The standard error for this result is 252.652, and the *z*-score is 6.919. This *z*-score is significant at $p < 0.0005$. This therefore finds a significant difference in the number of admissions after clozapine was initiated. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of admissions after starting clozapine.

The effect size (r) for this result can be calculated by dividing the *z*-score by the square root of the number of observations in the data set (this is double the number of patients in the data, since each patient was associated with two result scores) = 0.48. Using Cohen's criteria, this is a medium effect size (between 0.3 and 0.5).

5.3.1.2 Method 2

This method excludes the entire index admission:

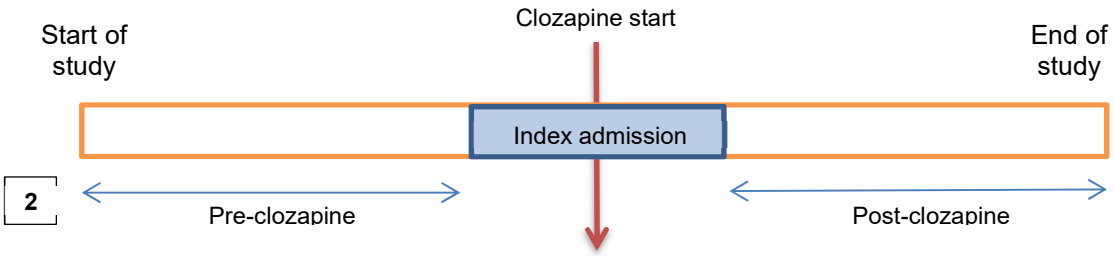

Figure 5-3 Method 2 analysis

Outcome data are presented in Table 5-5. Overall both the number of days spent as an inpatient per year and the number of total admissions per year were reduced after clozapine was started.

Table 5-5 Outcome data, intent to treat group, analysis method 2

Mean number of days of admission per year pre-clozapine	36.13
Mean number of days of admission per year post-clozapine	19.39
Mean number of admissions per year pre-clozapine	0.56
Mean number of admission per year post-clozapine	0.21
Net change in days of admission pre-post clozapine per year[a]	16.74
Net change in number of admissions pre/post clozapine per year[a]	0.34
Mean theoretical clozapine delay (years)	3.93

[a]negative number denotes higher number of days/admissions post-clozapine

5.3.1.2.1 Bias

As for method one, the scatter plot is presented in Appendix G (Figure 7-6 Scatterplot, intent to treat group, analysis method 2)and shows some outlying data points at both extremes of the primary outcome. On examination, these outliers occur due to the entire mirror image study period being entirely within one single admission, meaning that these patients are always inpatients (100% of the time spent both pre- and post-clozapine is as an inpatient). This introduces bias to the data set, as the reality for these patients is that much less than

100% of their total history is spent as an inpatient. This situation affects two cases. For two further cases either the pre- or the post-clozapine periods are entirely within one single admission. This bias will affect the estimate of the mean, the sum of the squared error and the standard deviation. These data cannot be trimmed from the data set as they are from the inclusion population.

The z-score results are also presented in Appendix G (Table 7-51), and indicate that 96.1% of the data points are within normal range. This is above the commonly accepted limits of 95%. I did not therefore go on to calculate skew and kurtosis for this data set.

5.3.1.2.2 Paired samples *t*-test

The paired samples *t*-test results for these data are presented in Appendix G (Table 7-51), and show a significant difference between the days of admission per year pre-clozapine and days of admission per year post-clozapine ($p = 0.004$). There is also a significant difference between the total number of admissions per year pre-clozapine and admissions per year post-clozapine ($p < 0.0005$).

5.3.1.3 Method 3

This method attributes the index admission up to the point of clozapine initiation to the pre-clozapine period, excluding the first 14 days of the post-clozapine period from analysis, and then attributing any remaining days in the index admission to the post-clozapine period.

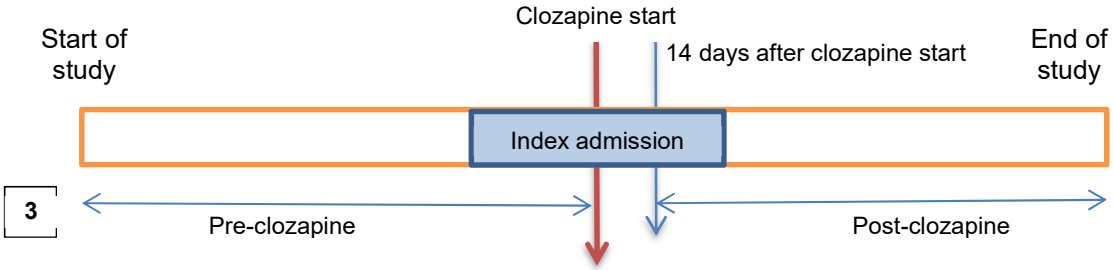

Figure 5-4 Method 3 analysis

Outcome data are presented in Table 5-6. Overall both the number of days spent as an inpatient per year and the number of total admissions per year were reduced after clozapine was started.

Table 5-6 Outcome data, intent to treat group, analysis method 3

		Bias			
		Kolmogorov-Smirnov		Shapiro-Wilk	
		$D_{(102)}$	*p*	$W_{(102)}$	*p*
Mean number of days of admission per year pre-clozapine	66.70				
Mean number of days of admission per year post-clozapine	64.28				
Mean number of admissions per year pre-clozapine	0.95				
Mean number of admission per year post-clozapine	0.21				
Net change in days of admission pre-post clozapine per year[a]	2.42	0.194	< 0.0005	0.886	< 0.0005
Net change in number of admissions pre/post clozapine per year[a]	0.73	0.200	< 0.0005	0.720	< 0.0005
Mean theoretical clozapine delay (years)	3.93	0.213	< 0.0005	0.791	< 0.0005

[a]negative number denotes higher number of days/admissions post-clozapine

5.3.1.3.1 Bias

As for methods 1 and 2, the scatter plot (shown for this data set in Appendix G, Figure 7-7) shows some outlying data points at both extremes of the primary outcome. On examination, these outliers occur due to the entire mirror image study period being entirely within one single admission, meaning that these patients are always inpatients (100% of the time spent both pre- and post-clozapine is as an inpatient). This introduces bias to the data set, as the reality for these patients is that much less than 100% of their total history is spent as an inpatient. This situation affects two cases. For two further cases either the pre- or the post-clozapine periods are entirely within one single admission. This bias will affect the estimate of the mean, the sum of the squared error and the standard deviation. These data cannot be trimmed from the data set as they are from the inclusion population.

The *z*-score results are presented in Appendix G (Table 7-53). For this data set, 1% of the cases were above 3.29 (extreme cases), 3.9% were greater than 2.58 (more than the expected 1% for probable outliers), and 2.9% had values greater than 1.96 (potential outliers). The remaining cases constitute 92.2% of the values, and these lie within the normal range. Therefore the data are not consistent with what would be expected from a normal distribution, where 95% of the data would be expected to fall with the normal range.

The investigations for skew and kurtosis are presented in Appendix G (Table 7-54). For the net change in the clozapine theoretical delay, the net change in the number of admissions per year and the total number of antipsychotics prescriptions used before clozapine, the skew is positive, indicating a concentration of data points on the left side of the distribution curve. For net change in days of admissions per year, the skew is negative but close to zero. All the measures show positive kurtosis, with the net change in number of admissions per year being the most affected. This indicates a heavy and pointy tailed distribution. All the values for z-skewness and z-kurtosis are above 3.29, meaning that they are significant at $p < 0.001$, indicating a problem with both skew and kurtosis in the data. I therefore went on to perform the Kolmogorov-Smirnov and Shapiro-Wilk tests, the results of which are presented in detail in Appendix G (Table 7-55), and above in Table 5-6.

From the Kolmogorov-Smirnov and Shapiro-Wilk tests, the scores for the net change in days of admission per year, net change in the number of admissions per year, total number of antipsychotic prescriptions before clozapine and the theoretical delay to starting clozapine are significantly non-normal (p <0.0005).

5.3.1.3.2 Wilcoxon signed rank test

As the data are not normally distributed, as shown by the tests above, I used the non-parametric Wilcoxon signed-rank test to establish differences in the change in days of admission per year pre- and post-clozapine. The result for this test is shown in Appendix G (Figure 7-8).

For the data on days of admission per year, there were 64 positive ranks, 32 negative ranks and 6 ties. The test score, T, is 2574.500. The standard error for this result is 2879.500, and the z-score is 2.015. This z-score is significant at $p = 0.044$. This therefore finds a significant difference in the number of days spent in hospital after clozapine was initiated. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of admissions after starting clozapine.

The effect size (r) for this result can be calculated by dividing the *z*-score by the square root of the number of observations in the data set = 0.14. Using Cohen's criteria, this is a small effect size (< 0.3).

I then repeated the test for the number of admissions per year before and after clozapine was started – again, the difference in admissions was calculated by taking the number of admissions per year post-clozapine away from the number of admissions per year pre-clozapine, and so a negative number denotes a larger number of admissions after clozapine had started. The results for this test are shown in Appendix G (Figure 7-9).

For these data there were 81 positive ranks, 10 negative ranks and 11 ties. The test score, *T*, is 3841. The standard error for this result is 252.652, and the *z*-score is 6.919. This *z*-score is significant at $p < 0.0005$. This therefore echoes the *t*-test result, finding a significant difference in the number of admissions after clozapine was initiated. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number admissions after starting clozapine.

The effect size (r) for this result can be calculated by dividing the *z*-score by the square root of the number of observations in the data set (this is double the number of patients in the data, since each patient was associated with two result scores) = 0.48. Using Cohen's criteria, this is a medium effect size (between 0.3 and 0.5).

5.3.1.4 Method 4

This method attributes the index admission pre-clozapine and the first 14 days of clozapine treatment to the pre-clozapine period, then attributing any remaining days of the index admission to the post-clozapine period.

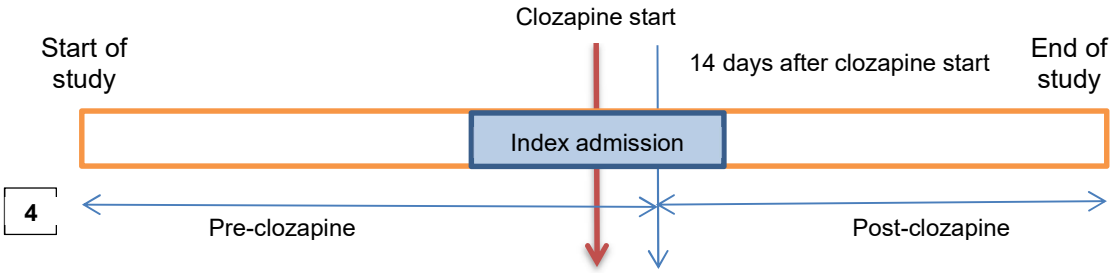

Figure 5-5 Method 4 analysis

Outcome data are presented in Table 5-7. Overall both the number of days spent as an inpatient per year and the number of total admissions per year were reduced after clozapine was started.

Table 5-7 Outcome data, intent to treat group, analysis method 4

Mean number of days of admission per year pre-clozapine	72.26
Mean number of days of admission per year post-clozapine	64.28
Mean number of admissions per year pre-clozapine	0.95
Mean number of admission per year post-clozapine	0.21
Net change in days of admission pre-post clozapine per year[a]	7.98
Net change in number of admissions pre/post clozapine per year[a]	0.73
Mean theoretical clozapine delay (years)	3.93

[a]negative number denotes higher number of days/admissions post-clozapine

5.3.1.4.1 Bias

The scatterplot for this data analysis is presented in Appendix G (Figure 7-10). As for methods 1, 2 and 3, the scatter plot shows some outlying data points at both extremes of the primary outcome. On examination, these outliers occur due to the entire mirror image study period being entirely within one single admission, meaning that these patients are always inpatients (100% of the time spent both pre- and post-clozapine is as an inpatient). This introduces bias to the data set, as the reality for these patients is that much less than 100% of their total history is spent as an inpatient. This situation affects two cases. For two further cases either the pre- or the post-clozapine periods are entirely within one single admission. This bias will affect the estimate of the mean, the sum of the squared error and the standard deviation. These data cannot be trimmed from the data set as they are from the inclusion population.

The *z*-score test data are shown in Appendix G (Table 7-56), and indicate that 97.1% of the data points are within normal range. This is above the commonly accepted limits of 95%, and so no further investigation of bias was required.

5.3.1.4.2 Paired samples *t*-test

The paired samples *t*-test results are given in Appendix G (Table 7-57), and show no significant difference between the days of admission per year pre-clozapine and days of admission per year post-clozapine ($p = 0.313$). There is a significant difference between the total number of admissions per year pre-clozapine and admissions per year post-clozapine ($p < 0.0005$).

5.3.1.5 Method 5

This method attributes the index admission up to the point of clozapine initiation to the pre-clozapine period, then excludes any remaining days of the index admission from analysis.

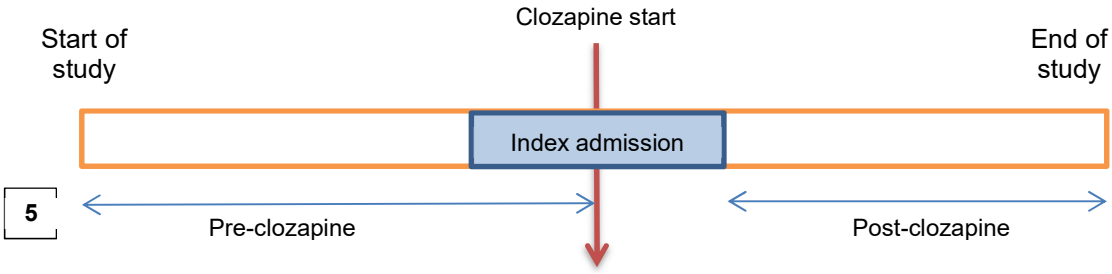

Figure 5-6 Method 5 analysis

Outcome data are presented in Table 5-8. Overall both the number of days spent as an inpatient per year and the number of total admissions per year were reduced after clozapine was started.

Table 5-8 Outcome data, intent to treat group, analysis method 5

		Bias			
		Kolmogorov-Smirnov		Shapiro-Wilk	
		$D_{(102)}$	*p*	$W_{(102)}$	*p*
Mean number of days of admission per year pre-clozapine	66.70				
Mean number of days of admission per year post-clozapine	19.39				
Mean number of admissions per year pre-clozapine	0.95				
Mean number of admission per year post-clozapine	0.21				
Net change in days of admission pre-post clozapine per year[a]	47.31	0.186	< 0.0005	0.829	< 0.0005
Net change in number of admissions pre/post clozapine per year[a]	0.73	0.200	< 0.0005	0.720	< 0.0005
Mean theoretical clozapine delay (years)	3.93	0.213	< 0.0005	0.791	< 0.0005

[a]negative number denotes higher number of days/admissions post-clozapine

5.3.1.5.1 Bias

The scatterplot for these data are presented in Appendix G (Figure 7-11), and as for methods 1, 2, 3 and 4, the scatterplot shows some outlying data points at both extremes of the primary outcome. On examination, these outliers occur due to the entire mirror image study period being entirely within one single admission, meaning that these patients are always inpatients (100% of the time spent both pre- and post-clozapine is as an inpatient). This introduces bias to the data set, as the reality for these patients is that much less than 100% of their total history is spent as an inpatient. This situation affects two cases. For two further cases either the pre- or the post-clozapine periods are entirely within one single admission. This bias will affect the estimate of the mean, the sum of the squared error and the standard deviation. These data cannot be trimmed from the data set as they are from the inclusion population.

The *z*-score results are presented in Appendix G (Table 7-58). For this data set, 2% of the cases were above 3.29 (extreme cases), 1% were greater than 2.58 (equal to the expected 1% for probable outliers), and 2.9% had values greater than 1.96 (potential outliers). The remaining cases constitute 92.2% of the values, and these lie within the normal range. Therefore overall the data are not consistent with what would be expected from a normal distribution, where 95% of the data would be expected to fall with the normal range.

The tests for skew and kurtosis are presented in Appendix G (Table 7-59). For the net change in the number of admissions and days of admission per year, the clozapine theoretical delay, and the total number of antipsychotics prescriptions used before clozapine, the skew is positive, indicating a concentration of data points on the left side of the distribution curve. All the measures show also show positive kurtosis, with the net change in number of admissions per year being the most affected. This indicates a heavy and pointy tailed distribution. All the values for z-skewness and z-kurtosis are above 3.29, meaning that they are significant at $p < 0.001$, indicating a problem with both skew and kurtosis in the data.

The tests for normality are presented in detail in Appendix G (Table 7-60) and above in Table 5-8. From the Kolmogorov-Smirnov and Shapiro-Wilk tests, scores for the net change in days of admission per year, net change in the number of admissions per year, total number of antipsychotic prescriptions before clozapine, and the theoretical delay to starting clozapine are significantly non-normal ($p < 0.0005$).

5.3.1.5.2 Wilcoxon signed rank test

As the data are not normally distributed, as shown by the tests above, I used the non-parametric Wilcoxon signed-rank test to establish differences in the change in days of admission per year pre- and post-clozapine. The result for this test is shown in Appendix G (Figure 7-12).

For the data on days of admission per year, there were 77 positive ranks, 19 negative ranks and 6 ties. The test score, *T*, is 3908.000. The standard error for this result is 273.649, and the *z*-score is 5.774. This *z*-score is significant at $p < 0.0005$. This therefore finds a significant difference in the number of days spent in hospital after clozapine was initiated. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of days of admission after starting clozapine.

The effect size (r) for this result can be calculated by dividing the *z*-score by the square root of the number of observations in the data set = 0.40. Using Cohen's criteria, this is a medium effect size (between 0.3 and 0.5).

I then repeated the test for the number of admissions per year before and after clozapine was started – again, the difference in admissions was calculated by taking the number of admissions per year post-clozapine away from the number of admissions per year pre-clozapine, and so a negative number denotes a larger number of admissions after clozapine had started. The results for this test are shown in Appendix G (Figure 7-13).

For these data there were 81 positive ranks, 10 negative ranks and 11 ties. The test score, *T*, is 3841. The standard error for this result is 252.652, and the *z*-score is 6.919. This *z*-score is significant at $p < 0.0005$. This therefore echoes the *t*-test result, finding a significant difference in the number of admissions after clozapine was initiated. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number admissions after starting clozapine.

The effect size (r) for this result can be calculated by dividing the *z*-score by the square root of the number of observations in the data set (this is double the number of patients in the data, since each patient was associated with two result scores) = 0.48. Using Cohen's criteria, this is a medium effect size (between 0.3 and 0.5).

5.3.1.6 Summary

Table 5-9 Intent to treat data, summary of normality of distributions and associated test results

	Data within normal range (%)	**Days of admission per year (*p*)**	**Admissions per year (*p*)**
Method 1	92.2	0.274[a]	< 0.0005[a]
Method 2	96.1	0.004[b]	< 0.0005[b]
Method 3	92.2	0.044[a]	< 0.0005[a]
Method 4	97.1	0.313[b]	< 0.0005[b]
Method 5	92.2	< 0.0005[a]	< 0.0005[a]

[a]Wilcoxon signed rank test
[b]Paired samples *t*-test

As shown in Table 5-9, when testing for normality of the data distributions, methods 2 and 4

contain data that lies >95% within the normal range (and would therefore be considered normal distributions). The statistical tests show that there is a statistically significant difference between days of admission per year pre- versus post-clozapine for methods 2, 3 and 5 only, but that all methods of analysis show a statistically significant difference in the number of admissions per year.

Calculation of *z*-scores for the intent to treat population for the different analysis methods shows that for methods 2 and 4, more than 95% of the data fall within the normal range. For the other methods, 92.2% of the data fall within the normal range, below the usually accepted standard of 95%. The data cannot be trimmed of outliers as they do represent part of the true sample population. They will bias the estimates of the mean and affect the sum of the squared errors, and therefore the confidence intervals around the mean.

Other reasons for the bias may be a violation of the assumption of normality. If in fact the clozapine continuers and discontinuers should be considered as two different populations, then by combining them a bimodal distribution may occur. However, the central limit theorem generally allows for sample sizes above 30 to produce a sampling distribution that approximates normal. With a sample size of 102, as in this data set, the central limit theorem may apply provided the sample is not too severely skewed or subject to kurtosis. The Kolmogorov-Smirnov and Shapiro-Wilk tests of normality of the distribution have been explained previously, and the results of these tests show that the data distribution is significantly non-normal. This result is supported by positive skew scores for net change in days of admission pre- and post-clozapine use for all methods of data analysis, and positive kurtosis scores for the same. Skew is negative for net change in numbers of days of admission pre- and post-clozapine use, but positive for numbers of admissions per year. However – tests for skew, kurtosis and normality are less useful when considering large data sets. They are more likely to produce a significant result even for small and unimportant effects. As mentioned above, the central limit theorem means that the assumption of normality matters less for larger sample sizes, because the sampling distribution will be normal regardless of the sample data.

Table 5-10 gives a summary of the data analysis for the intent to treat population. For all methods of data analysis, there was a significant reduction in the total number of admissions per year after clozapine was started. The majority of data analysis methods (2, 3 and 5) also showed a significant reduction in the number of days per year spent as an inpatient.

Table 5-10 Intent to treat data summary

	Mean number of days of admission per year		Mean number of admissions per year				
	Pre-clozapine	Post-clozapine	Pre-clozapine	Post-clozapine	Net change in days of admission pre-post clozapine per year[a]	Net change in number of admissions pre/post clozapine per year[b]	Mean theoretical clozapine delay (years)
Method 1	66.7	69.69	0.95	0.21	-2.98	0.73	3.93
	$p = 0.274$		$p < 0.0005$				
Method 2	36.13	19.39	0.56	0.21	16.74	0.34	3.93
	$p = 0.004$		$p < 0.0005$				
Method 3	66.7	64.28	0.95	0.21	2.42	0.73	3.93
	$p = 0.044$		$p < 0.0005$				
Method 4	72.26	64.28	0.95	0.21	7.98	0.73	3.93
	$p = 0.313$		$p < 0.0005$				
Method 5	66.7	19.39	0.95	0.21	47.31	0.73	3.93
	$p < 0.0005$		$p < 0.0005$				

[a]negative number denotes higher number of days post-clozapine
[b]negative number denotes higher number of admissions post-clozapine

5.3.2 Clozapine continuers

Having presented the data analysis for the intent to treat population above, I have repeated this analysis separately for patients who continued clozapine (clozapine continuers) and patients who discontinued clozapine (clozapine discontinuers). The demographic data for clozapine continuers are presented in Table 5-3 above.

5.3.2.1 Method 1

This method is a simple mirror image division, where days of admission before clozapine are attributed to the pre-clozapine period, and days of admission after clozapine are attributed to the post-clozapine period (see Figure 5-2).

Outcome data are presented in Table 5-11. Overall both the number of days spent as an inpatient per year and the number of total admissions per year were reduced after clozapine was started.

Table 5-11 Outcome data, clozapine continuers group, analysis method 1

Mean number of days of admission per year pre-clozapine	64.29
Mean number of days of admission per year post-clozapine	51.89
Mean number of admissions per year pre-clozapine	0.88
Mean number of admission per year post-clozapine	0.11
Net change in days of admission pre-post clozapine per year (negative number denotes higher number of days post-clozapine)	12.40
Net change in number of admissions pre/post clozapine per year (negative number denotes higher number of admissions post-clozapine)	0.77
Mean theoretical clozapine delay (years)	4.13

5.3.2.1.1 Bias

For this data analysis I first examined normal quantile-quantile (Q-Q plots) to assess normality within the distribution. The Q-Q plot for this data analysis is presented in Appendix G (Figure 7-14). The Q-Q plot plots the cumulative probability of a variable against the cumulative probability of a particular distribution (in the case of these data, a normal distribution). Z-scores are calculated from the data (as described previously), and this score plotted against the z-score that would be expected if the distribution was normal. If the data are distributed normally, then the plot will be a straight line (shown for reference on the graph). The actual data z-scores are plotted against this line (shown as round circles), and any deviation of the z-scores from the line of normality therefore demonstrates problems in this regard. Where data points sag above or below the normal line, kurtosis differs from the normal distribution. Where the data points form an S-shaped curve, the data are skewed. The Q-Q plot presented here suggests a problem with kurtosis and skew. The sample size for this analysis is smaller than that for the intent to treat analysis, although still larger than

that which is generally considered to adhere to normality under the central limit theorem. Nonetheless, due to the smaller sample size I have followed up paired sample *t*-tests with further non-parametric equivalent tests to account for the smaller sample size and to ensure a significant result is not missed by the parametric test.

5.3.2.1.2 Paired samples *t*-test

A paired samples *t*-test was conducted as described previously (the results of which are presented in Appendix G, Table 7-61), and this shows no significant difference between the days of admission per year pre-clozapine and days of admission per year post-clozapine ($p = 0.107$). There is a significant difference between the total number of admissions per year pre-clozapine and admissions per year post-clozapine ($p < 0.0005$).

5.3.2.1.3 Wilcoxon signed rank test

For the data on days of admission per year, there were 44 positive ranks, 19 negative ranks and 4 ties (where the number of days of admission was the same before and after clozapine). The test score, T, is 1443.000 (see Appendix G, Figure 7-15). The standard error for this result is 146.068, and the z-score is 2.978. This z-score is significant at p = 0.03. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of days of admission after starting clozapine.

The effect size (r) for this result can be calculated by dividing the *z*-score by the square root of the number of observations in the data set (this is double the number of patients in the data, since each patient was associated with two result scores) = 0.257. Using Cohen's criteria, this is a small effect size (< 0.3).

For the difference in admissions, the histogram (presented in Appendix G, Figure 7-16) shows that there were 59 positive ranks, 4 negative ranks and 4 ties. The test score, T, is 1944.000. The standard error for this result is 146.062, and the z-score is 6.408. This z-score is significant at p < 0.0005. From the histogram, it is clear that this test statistic is

based on there being more positive differences than negative differences; therefore there was a significant decrease in the number of admissions after starting clozapine.

The effect size (r) for this result can be calculated by dividing the *z*-score by the square root of the number of observations in the data set = 0.277. Using Cohen's criteria, this is a small effect size (< 0.3).

5.3.2.2 Method 2

This method excludes the entire index admission from analysis (see Figure 5-3).

Outcome data are presented in Table 5-12. Overall both the number of days spent as an inpatient per year and the number of total admissions per year were reduced after clozapine was started.

Table 5-12 Outcome data, clozapine continuers group, analysis method 2

Mean number of days of admission per year pre-clozapine	34.70
Mean number of days of admission per year post-clozapine	9.97
Mean number of admissions per year pre-clozapine	0.50
Mean number of admission per year post-clozapine	0.12
Net change in days of admission pre-post clozapine per year (negative number denotes higher number of days post-clozapine)	24.73
Net change in number of admissions pre/post clozapine per year (negative number denotes higher number of admissions post-clozapine)	1.42
Mean theoretical clozapine delay (years)	4.13

5.3.2.2.1 Bias

As for method 1, I first examined normal quantile-quantile (Q-Q plots) to assess normality within the distribution. The Q-Q plot for this data analysis is presented in Appendix G (Figure 7-17). The Q-Q plot presented here suggests a problem with kurtosis and skew.

5.3.2.2.2 Paired samples *t*-test

A paired samples *t*-test was conducted as described previously (the results of which are presented in Appendix G, Table 7-62Table 7-62), and this shows a significant difference between admission days per year pre-clozapine and admission days per year post-clozapine

($p < 0.0005$). There is also a significant difference between admissions per year pre-clozapine and admissions per year post-clozapine ($p < 0.0005$).

5.3.2.2.3 Wilcoxon signed-rank test

The histogram and associated data table are shown in Appendix G (Figure 7-18). For the difference in days of admission per year, there were 42 positive ranks, 8 negative ranks and 17 ties. The test score, T, is 1109.000. The standard error for this result is 103.592, and the z-score is 4.552. This z-score is significant at $p < 0.0005$. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of days of admission after starting clozapine.

The effect size (r) is 0.39. Using Cohen's criteria, this is a medium effect size (between 0.3 and 0.5).

For the difference in admissions per year (see Appendix G, Figure 7-19), there were 44 positive ranks, 5 negative ranks and 18 ties. The test score, T, is 1129.000. The standard error for this result is 100.525, and the z-score is 5.138. This z-score is significant at $p < 0.0005$. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of admissions after starting clozapine.

The effect size (r) is 0.22. Using Cohen's criteria, this is a small effect size (< 0.3).

5.3.2.3 Method 3

This method attributes the index admission up to the point of clozapine initiation to the pre-clozapine period, excluding the first 14 days of the post-clozapine period from analysis, and then attributes any remaining days in the index admission to the post-clozapine period (see Figure 5-4).

Outcome data are presented in Table 5-13. Overall both the number of days spent as an inpatient per year and the number of total admissions per year were reduced after clozapine was started.

Table 5-13 Outcome data, clozapine continuers group, analysis method 3

Mean number of days of admission per year pre-clozapine	64.29
Mean number of days of admission per year post-clozapine	46.59
Mean number of admissions per year pre-clozapine	0.88
Mean number of admission per year post-clozapine	0.12
Net change in days of admission pre-post clozapine per year (negative number denotes higher number of days post-clozapine)	17.70
Net change in number of admissions pre/post clozapine per year (negative number denotes higher number of admissions post-clozapine)	0.77
Mean theoretical clozapine delay (years)	4.13

5.3.2.3.1 Bias

As for method 1, I first examined normal quantile-quantile (Q-Q plots) to assess normality within the distribution. The Q-Q plot for this data analysis is presented in Appendix G (Figure 7-20). The Q-Q plot presented here suggests a problem with kurtosis and skew.

5.3.2.3.2 Paired samples t-test

A paired samples *t*-test was conducted as described previously (the results of which are presented in Appendix G, Table 7-63), and this shows a significant difference between days of admission per year pre-clozapine and days of admission per year post-clozapine ($p = 0.025$). There is a significant difference between admissions per year pre-clozapine and admissions per year post-clozapine ($p < 0.0005$).

5.3.2.3.3 Wilcoxon signed-rank test

The histogram and associated data table are shown in Appendix G (Figure 7-21). For the data on days of admission per year, there were 13 negative ranks, 51 positive ranks and 3 ties. The test score, T, is 1577.000. The standard error for this result is 149.533, and the z-score is 3.591. This z-score is significant at $p < 0.0005$. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of days of admission after starting

clozapine. The effect size (r) is 0.16. Using Cohen's criteria, this is a small effect size (< 0.3).

The histogram and associated data table are shown in Appendix G (Figure 7-22) for the change in admissions per year after starting clozapine. For these data there were 4 negative ranks, 59 positive ranks and 4 ties. The test score, T, is 1944.000. The standard error for this result is 146.062, and the z-score is 6.408. This z-score is significant at $p < 0.0005$. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of admissions after starting clozapine. The effect size (r) is 0.23. Using Cohen's criteria, this is a small effect size (< 0.3)

5.3.2.4 Method 4

This method attributes the index admission pre-clozapine and the first 14 days of clozapine treatment to the pre-clozapine period, then attributes any remaining days of the index admission to the post-clozapine period.

Outcome data are presented in Table 5-14. Overall both the number of days spent as an inpatient per year and the number of total admissions per year were reduced after clozapine was started.

Table 5-14 Outcome data, clozapine continuers group, analysis method 4

Mean number of days of admission per year pre-clozapine	69.78
Mean number of days of admission per year post-clozapine	46.59
Mean number of admissions per year pre-clozapine	0.88
Mean number of admissions per year post-clozapine	0.12
Net change in days of admission pre-post clozapine per year (negative number denotes higher number of days post-clozapine)	23.19
Net change in number of admissions pre/post clozapine per year (negative number denotes higher number of admissions post-clozapine)	0.77
Mean theoretical clozapine delay (years)	4.13

5.3.2.4.1 Bias

As for method 1, I first examined normal quantile-quantile (Q-Q plots) to assess normality within the distribution. The Q-Q plot for this data analysis is presented in Appendix G (Figure 7-23). The Q-Q plot presented here suggests a problem with kurtosis and skew.

5.3.2.4.2 Paired samples t-test

A paired samples *t*-test was conducted as described previously (the results of which are presented in Appendix G, Table 7-64), and this shows a significant difference between days of admission per year pre-clozapine and days of admission per year post-clozapine (p = 0.007). There is a significant difference between admissions per year pre-clozapine and admissions per year post-clozapine ($p < 0.0005$).

5.3.2.4.3 Wilcoxon signed-rank test

The histogram and associated data table are shown in Appendix G (Figure 7-24). For the data on days of admission per year, there were 53 positive ranks, 12 negative ranks and 2 ties. The test score, T, is 1664.000. The standard error for this result is 153.024, and the z-score is 3.865. This z-score is significant at $p < 0.0005$. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of days of admission after starting clozapine. The effect size (r) is 0.33. Using Cohen's criteria, this is a medium effect size (between 0.3 and 0.5).

The histogram and associated data table are shown in Appendix G (Figure 7-25) for the change in admissions per year after starting clozapine. For these data there were 4 negative ranks, 59 positive ranks and 4 ties. The test score, T, is 1944.000. The standard error for this result is 146.062, and the z-score is 6.408. This z-score is significant at $p < 0.0005$. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of admissions after starting clozapine. The effect size (r) is 0.23. Using Cohen's criteria, this is a small effect size (< 0.3).

5.3.2.5 Method 5

This method attributes the index admission up to the point of clozapine initiation to the pre-clozapine period, then excludes any remaining days of the index admission from analysis (Figure 5-6).

Outcome data are presented in Table 5-15. Overall both the number of days spent as an inpatient per year and the number of total admissions per year were reduced after clozapine was started.

Table 5-15 Outcome data, clozapine continuers group, analysis method 5

Mean number of days of admission per year pre-clozapine	64.29
Mean number of days of admission per year post-clozapine	9.97
Mean number of admissions per year pre-clozapine	0.88
Mean number of admission per year post-clozapine	0.11
Net change in days of admission pre-post clozapine per year (negative number denotes higher number of days post-clozapine)	54.32
Net change in number of admissions pre/post clozapine per year (negative number denotes higher number of admissions post-clozapine)	0.77
Mean theoretical clozapine delay (years)	4.13

5.3.2.5.1 Bias

As for method 1, I first examined normal quantile-quantile (Q-Q plots) to assess normality within the distribution. The Q-Q plot for this data analysis is presented in Appendix G (Figure 7-26). The Q-Q plot presented here suggests a problem with kurtosis and skew.

5.3.2.5.2 Paired samples t-test

A paired samples *t*-test was conducted as described previously (the results of which are presented in Appendix G, Table 7-65), and this shows a significant difference between days of admission per year pre-clozapine and days of admission per year post-clozapine ($p < 0.0005$). There is also a significant difference between admissions per year pre-clozapine and admissions per year post-clozapine ($p < 0.0005$).

5.3.2.5.3 Wilcoxon signed-rank test

The histogram and associated data table are shown in Appendix G (Figure 7-27). For the data on days of admission per year, there were 59 positive ranks, 5 negative ranks and 3

ties. The test score, T, is 1957.000. The standard error for this result is 149.593, and the z-score is 6.132. This z-score is significant at $p < 0.0005$. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of days of admission after starting clozapine. The effect size (r) is 0.26. Using Cohen's criteria, this is a small effect size (< 0.3).

The histogram and associated data table are shown in Appendix G (Figure 7-28) for the change in admissions per year after starting clozapine. For these data there were 4 negative ranks, 59 positive ranks and 4 ties. The test score, T, is 1944.000. The standard error for this result is 146.062, and the z-score is 6.408. This z-score is significant at $p < 0.0005$. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of admissions after starting clozapine. The effect size (r) is 0.23. Using Cohen's criteria, this is a small effect size (< 0.3).

Table 5-16 Clozapine continuers data summary

	Mean number of days of admission per year		Mean number of admissions per year				
	Pre-clozapine	Post-clozapine	Pre-clozapine	Post-clozapine	Net change in days of admission pre-post clozapine per year[a]	Net change in number of admissions pre/post clozapine per year[b]	Mean theoretical clozapine delay (years)
Method 1	64.29	51.89	0.88	0.11	12.4	0.77	4.13
	p =0.03		p < 0.0005				
Method 2	34.7	9.97	0.5	0.12	24.73	1.42	4.13
	p < 0.0005		p < 0.0005				
Method 3	64.29	46.59	0.88	0.12	17.7	0.77	4.13
	p < 0.0005		p < 0.0005				
Method 4	69.78	46.59	0.88	0.12	23.19	0.77	4.13
	p < 0.0005		p < 0.0005				
Method 5	64.29	9.97	0.88	0.11	54.32	0.77	4.13
	p < 0.0005		p < 0.0005				

[a]negative number denotes higher number of days post-clozapine
[b]negative number denotes higher number of admissions post-clozapine

Table 5-16 shows that there is a statistically significant difference between the number of days of admission pre- and post-clozapine for all methods of data analysis. There is also a statistically significant difference between the number of admissions pre- and post-clozapine for all methods. Note that the mean clozapine delay is numerically longer for clozapine continuers than for clozapine discontinuers, but this difference is not statistically significant (*t*-test = 0.626, *p* = 0.533).

If patients keep taking clozapine, then no matter how you look at the data, they have fewer admissions per year and days per year as an inpatient when they are taking the clozapine compared to before they were taking the clozapine. However, the magnitude of this difference differs depending on the analysis method.

5.3.3 Clozapine discontinuers

5.3.3.1 Method 1

This is a simple mirror image division, whereby days of admission before clozapine are attributed to the pre-clozapine period, and days of admission after clozapine are attributed to the post-clozapine period (see Figure 5-2). Demographic data for this group are presented in Table 5-3.

Outcome data are presented in Table 5-17. Overall there was an increase in the number of days spent as an inpatient after clozapine had started, but a reduction in the total number of admissions per year.

Table 5-17 Outcome data, clozapine discontinuers group, analysis method 1

Mean number of days of admission per year pre-clozapine	71.33
Mean number of days of admission per year post-clozapine	103.76
Mean number of admissions per year pre-clozapine	1.08
Mean number of admission per year post-clozapine	0.41
Net change in days of admission pre-post clozapine per year (negative number denotes higher number of days post-clozapine)	-32.43
Net change in number of admissions pre/post clozapine per year (negative number denotes higher number of admissions post-clozapine)	0.66
Mean theoretical clozapine delay (years)	3.53

5.3.3.1.1 Bias

As described for clozapine continuers, I first examined normal quantile-quantile (Q-Q plots) to assess normality within the distribution. The Q-Q plot for this data analysis is presented in Appendix G (Figure 7-29). The Q-Q plot presented here suggests a problem with kurtosis and skew.

5.3.3.1.2 Paired samples t-test

A paired samples *t*-test was conducted as described previously (the results of which are presented in Appendix G, Table 7-66), and this shows a significant difference between the days of admission per year pre-clozapine and days of admission per year post-clozapine (p = 0.040). There is also a significant difference between the total number of admissions per year pre-clozapine and admissions per year post-clozapine (p = 0.002).

5.3.3.1.3 Wilcoxon signed-rank test

The histogram and associated data table are shown in Appendix G (Figure 7-30). For the data for days of admission per year there were 11 positive ranks, 21 negative ranks and 3 ties. The test score, *T*, is 150.000. The standard error for this result is 53.479, and the *z*-score is 2.132. This *z*-score is significant at p = 0.033. From the histogram, it is clear that this test statistic is based on there being more negative differences than positive differences, therefore there was a significant increase in the number of days of admission after starting clozapine. The effect size (r) is 0.255. Using Cohen's criteria, this is a small effect size (below 0.3).

The histogram and associated data table are shown in Appendix G (Figure 7-31) for the change in admissions per year after starting clozapine. For these data there were 6 negative ranks, 22 positive ranks and 7 ties. The test score, *T*, is 337.500. The standard error for this result is 43.912, and the *z*-score is 3.063. This *z*-score is significant at p = 0.002. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of

admissions after starting clozapine. The effect size (r) is 0.37. Using Cohen's criteria, this is a medium effect size (between 0.3 and 0.5).

5.3.3.2 Method 2

This method excludes the entire index admission (see Figure 5-3).

Outcome data are presented in Table 5-18. Overall both the number of days spent as an inpatient per year and the number of total admissions per year were reduced after clozapine was started.

Table 5-18 Outcome data, clozapine discontinuers group, analysis method 2

Mean number of days of admission per year pre-clozapine	38.85
Mean number of days of admission per year post-clozapine	37.43
Mean number of admissions per year pre-clozapine	0.67
Mean number of admission per year post-clozapine	0.41
Net change in days of admission pre-post clozapine per year (negative number denotes higher number of days post-clozapine)	1.42
Net change in number of admissions pre/post clozapine per year (negative number denotes higher number of admissions post-clozapine)	0.25
Mean theoretical clozapine delay (years)	3.53

5.3.3.2.1 Bias

As described for clozapine continuers, I first examined normal quantile-quantile (Q-Q plots) to assess normality within the distribution. The Q-Q plot for this data analysis is presented in Appendix G (Figure 7-32). The Q-Q plot presented here suggests a problem with kurtosis and skew.

5.3.3.2.2 Paired samples t-test

A paired samples *t*-test was conducted as described previously (the results of which are presented in Appendix G, Table 7-67), and this shows no significant difference between admission days per year pre-clozapine and admission days per year post-clozapine (p = 0.906). There is also no significant difference between admissions per year pre-clozapine and admissions per year post-clozapine (p = 0.78).

5.3.3.2.3 Wilcoxon signed-rank test

The histogram and associated data table are shown in Appendix G (Figure 7-33). For these data there were 16 positive ranks, 15 negative ranks and 4 ties. The test score, *T*, is 255.000. The standard error for this result is 51.029, and the *z*-score is 0.137. This *z*-score is non-significant at $p = 0.891$.

The histogram and associated data table are shown in Appendix G (Figure 7-34) for the change in admissions per year after starting clozapine. For these data there were 10 negative ranks, 16 positive ranks and 9 ties. The test score, *T*, is 237.000. The standard error for this result is 39.372, and the *z*-score is 1.562. This *z*-score is non-significant at $p = 0.118$.

5.3.3.3 Method 3

This method attributes the index admission up to the point of clozapine initiation to the pre-clozapine period, excludes the first 14 days of the post-clozapine period from analysis, and then attributes any remaining days in the index admission to the post-clozapine period.

Outcome data are presented in Table 5-19. Overall there was an increase in the number of days spent as an inpatient after clozapine had started, but a reduction in the total number of admissions per year.

Table 5-19 Outcome data, clozapine discontinuers group, analysis method 3

Mean number of days of admission per year pre-clozapine	71.33
Mean number of days of admission per year post-clozapine	98.15
Mean number of admissions per year pre-clozapine	1.08
Mean number of admission per year post-clozapine	0.41
Net change in days of admission pre-post clozapine per year (negative number denotes higher number of days post-clozapine)	-26.81
Net change in number of admissions pre/post clozapine per year (negative number denotes higher number of admissions post-clozapine)	0.66
Mean theoretical clozapine delay (years)	3.53

5.3.3.3.1 Bias

As described for clozapine continuers, I first examined normal quantile-quantile (Q-Q plots) to assess normality within the distribution. The Q-Q plot for this data analysis is presented

in Appendix G (Figure 7-35). The Q-Q plot presented here suggests a problem with kurtosis and skew.

5.3.3.3.2 Paired samples t-test

A paired samples *t*-test was conducted as described previously (the results of which are presented in Appendix G, Table 7-68), and this shows no significant difference between days of admission per year pre-clozapine and days of admission per year post-clozapine (p = 0.088). There is a significant difference between admissions per year pre-clozapine and admissions per year post-clozapine (p = 0.002).

5.3.3.3.3 Wilcoxon signed-rank test

The histogram and associated data table are shown in Appendix G (Figure 7-36). For the data for days of admission per year there were 13 positive ranks, 19 negative ranks and 3 ties. The test score, *T*, is 190.000. The standard error for this result is 53.479, and the *z*-score is -1.384. This *z*-score is non-significant at p = 0.166.

The histogram and associated data table are shown in Appendix G (Figure 7-37) for the change in admissions per year after starting clozapine. For these data there were 6 negative ranks, 22 positive ranks and 7 ties. The test score, *T*, is 337.500. The standard error for this result is 43.912, and the *z*-score is 3.063. This *z*-score is significant at p = 0.002. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of admissions after starting clozapine. The effect size (r) is 0.37. Using Cohen's criteria, this is a medium effect size (between 0.3 and 0.5).

5.3.3.4 Method 4

This method attributes the index admission pre-clozapine and the first 14 days of clozapine treatment to the pre-clozapine period, then attributes any remaining days of the index admission to the post-clozapine period.

Outcome data are present in Table 5-20. Overall there was an increase in the number of days spent as an inpatient after clozapine had started, but a reduction in the total number of admissions per year.

Table 5-20 Outcome data, clozapine discontinuers group, analysis method 4

Mean number of days of admission per year pre-clozapine	77.01
Mean number of days of admission per year post-clozapine	98.15
Mean number of admissions per year pre-clozapine	1.08
Mean number of admissions per year post-clozapine	0.41
Net change in days of admission pre-post clozapine per year (negative number denotes higher number of days post-clozapine)	-21.14
Net change in number of admissions pre/post clozapine per year (negative number denotes higher number of admissions post-clozapine)	0.66
Mean theoretical clozapine delay (years)	3.53

5.3.3.4.1 Bias

As described for clozapine continuers, I first examined normal quantile-quantile (Q-Q plots) to assess normality within the distribution. The Q-Q plot for this data analysis is presented in Appendix G (Figure 7-38). The Q-Q plot presented here suggests a problem with kurtosis and skew.

5.3.3.4.2 Paired samples t-test

A paired samples *t*-test was conducted as described previously (the results of which are presented in Appendix G, Table 7-69), and this shows no significant difference between days of admission per year pre-clozapine and days of admission per year post-clozapine (p = 0.181). There is a significant difference between admissions per year pre-clozapine and admissions per year post-clozapine (p = 0.002).

5.3.3.4.3 Wilcoxon signed-rank test

The histogram and associated data table are shown in Appendix G (Figure 7-39). For these data there were 13 positive ranks, 19 negative ranks and 3 ties. The test score, *T*, is 204.000. The standard error for this result is 53.479, and the *z*-score is -1.122. This *z*-score is non-significant at p = 0.262.

The histogram and associated data table are shown in Appendix G (Figure 7-40) for the change in admissions per year after starting clozapine. For these data there were 6 negative ranks, 22 positive ranks and 7 ties. The test score, *T*, is 337.500. The standard error for this result is 43.912, and the *z*-score is 3.063. This *z*-score is significant at $p = 0.002$. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of admissions after starting clozapine. The effect size (r) is 0.37. Using Cohen's criteria, this is a medium effect size (between 0.3 and 0.5).

5.3.3.5 Method 5

This method attributes the index admission up to the point of clozapine initiation to the pre-clozapine period, then excludes any remaining days of the index admission from analysis (see Figure 5-6).

Outcome data are presented in Table 5-21. Overall both the number of days spent as an inpatient per year and the number of total admissions per year were reduced after clozapine was started.

Table 5-21 Outcome data, clozapine discontinuers group, analysis method 5

Mean number of days of admission per year pre-clozapine	71.33
Mean number of days of admission per year post-clozapine	37.43
Mean number of admissions per year pre-clozapine	1.08
Mean number of admission per year post-clozapine	0.41
Net change in days of admission pre-post clozapine per year (negative number denotes higher number of days post-clozapine)	33.90
Net change in number of admissions pre/post clozapine per year (negative number denotes higher number of admissions post-clozapine)	0.66
Mean theoretical clozapine delay (years)	3.53

5.3.3.5.1 Bias

As described for clozapine continuers, I first examined normal quantile-quantile (Q-Q plots) to assess normality within the distribution. The Q-Q plot for this data analysis is presented in Appendix G (Figure 7-41). The Q-Q plot presented here suggests a problem with kurtosis and skew.

5.3.3.5.2 Paired samples t-test

A paired samples *t*-test was conducted as described previously (the results of which are presented in Appendix G, Table 7-70), and this shows no significant difference between days of admission per year pre-clozapine and days of admission per year post-clozapine (p = 0.083). There is a significant difference between admissions per year pre-clozapine and admissions per year post-clozapine (p = 0.002).

5.3.3.5.3 Wilcoxon signed-rank test

The histogram and associated data table are shown in Appendix G (Figure 7-42). For these data there were 18 positive ranks, 14 negative ranks and 3 ties. The test score, *T*, is 339.000. The standard error for this result is 53.479, and the *z*-score is 1.402. This *z*-score is non-significant at p = 0.161.

The histogram and associated data table are shown in Appendix G (Figure 7-43) for the change in admissions per year after starting clozapine. For these data there were 6 negative ranks, 22 positive ranks and 7 ties. The test score, *T*, is 337.500. The standard error for this result is 43.912, and the *z*-score is 3.063. This *z*-score is significant at p = 0.002. From the histogram, it is clear that this test statistic is based on there being more positive differences than negative differences, therefore there was a significant decrease in the number of admissions after starting clozapine. The effect size (r) is 0.37. Using Cohen's criteria, this is a medium effect size (between 0.3 and 0.5).

Table 5-22 Clozapine discontinuers data summary

	Mean number of days of admission per year		Mean number of admissions per year				
	Pre-clozapine	**Post-clozapine**	**Pre-clozapine**	**Post-clozapine**	**Net change in days of admission pre-post clozapine per year[a]**	**Net change in number of admissions pre/post clozapine per year[b]**	**Mean theoretical clozapine delay (years)**
Method 1	71.33	103.76	1.08	0.41	-32.43	0.66	3.53
	p =0.033		*p* = 0.002				
Method 2	38.85	37.43	0.67	0.41	1.42	0.25	3.53
	p = 0.891		*p* = 0.118				
Method 3	71.33	98.15	1.08	0.41	-26.82	0.66	3.53
	p = 0.116		*p* = 0.002				
Method 4	77.01	98.15	1.08	0.41	-21.14	0.66	3.53
	p = 0.262		*p* = 0.002				
Method 5	71.33	37.43	1.08	0.41	33.90	0.66	3.53
	p = 0.161		*p* = 0.002				

[a] negative number denotes higher number of days post-clozapine
[b] negative number denotes higher number of admissions post-clozapine

Table 5-22 shows that there is a statistically significant difference between the mean number of days of admission per year pre- and post-clozapine for method 1 only. This is the only method to attribute the entire post-clozapine index admission period to the post-clozapine data count. The data show an increase in days spent in hospital after clozapine has been started; the opposite result to that found for clozapine continuers.

Table 5-22 also shows that for clozapine discontinuers, there is a statistically significant difference between the mean number of admissions per year pre- and post-clozapine for all methods except method 2 – this method is the only one to entirely exclude the index admission. For all the statistically significant results, a reduction in numbers of admissions per year after clozapine was started is shown.

5.3.4 Summary of clozapine continuers versus discontinuers

Table 5-23 Wilcoxon signed rank test summary for clozapine continuers versus discontinuers

	Effect on days of admission per year after clozapine started						**Effect on numbers of admissions per year after clozapine started**					
	Clozapine continuers			**Clozapine discontinuers**			**Clozapine continuers**			**Clozapine discontinuers**		
	p	**Effect size**	**Effect**	***p***	**Effect size**	**Effect**	***p***	**Effect size**	**Effect**	***p***	**Effect size**	**Effect**
Method 1	0.003	0.257	Decrease	0.033	0.255	Increase	< 0.0005	0.277	Decrease	0.002	0.37	Decrease
Method 2	< 0.0005	0.39	Decrease	0.891	N/A	No effect	< 0.0005	0.22	Decrease	0.118	N/A	No effect
Method 3	< 0.0005	0.16	Decrease	0.166	N/A	No effect	< 0.0005	0.23	Decrease	0.002	0.37	Decrease
Method 4	< 0.0005	0.33	Decrease	0.262	N/A	No effect	< 0.0005	0.23	Decrease	0.002	0.37	Decrease
Method 5	< 0.0005	0.26	Decrease	0.161	N/A	No effect	< 0.0005	0.23	Decrease	0.002	0.37	Decrease

Table 5-23 summarises the data set out above. For all methods of analysis for clozapine continuers, there is a change in the number of days spent as an inpatient once clozapine has been started. This change in the number of days of admission per year is only seen in the first analysis method for clozapine discontinuers; for all other methods of data analysis for discontinuers there was no change in the number of days of admission after the clozapine start date. For both clozapine continuers and discontinuers, there was an effect on the total number of admissions per year. This was regardless of the method of data analysis used, except for method 2 for discontinuers (no significant change).

For method 1 clozapine continuers, days of admission were significantly higher before starting clozapine (Mdn = 41.24) than after starting clozapine (Mdn = 11.65), T = 1443, p = 0.003, r = 0.257 (Table 5-23). However, for clozapine discontinuers, days of admission were significantly lower before starting clozapine (Mdn = 31.44) than after starting clozapine (Mdn = 62.69), T = 150, p = 0.033, r = 0.255. For clozapine continuers, the number of admissions was also significantly higher before starting clozapine (Mdn = 0.58) than after starting clozapine (Mdn =0.00), T = 1944, p < 0.0005, r = 0.277. This was also true for those that discontinued clozapine, with the number of admissions being significantly higher before starting clozapine (Mdn = 0.82) than after starting clozapine (Mdn = 0.28), T = 337.5, p = 0.002, r = 0.37.

For method 2 clozapine continuers, days of admission were significantly higher before starting clozapine (Mdn = 18.64) than after starting clozapine (Mdn = 0.00), T = 1109, p = <0.0005, r = 0.39. However, for clozapine discontinuers, days of admission were not statistically significantly different before starting clozapine (Mdn = 20.34) than after starting clozapine (Mdn = 17.87), T = 255, p = 0.891. For clozapine continuers, the number of admissions was also significantly higher before starting clozapine (Mdn = 0.40) than after starting clozapine (Mdn =0.00), T = 1129, p < 0.0005, r = 0.22. For those that discontinued clozapine, the number of admissions was not significantly different before starting clozapine (Mdn = 0.50) compared with after starting clozapine (Mdn = 0.28), T = 237, p = 0.118.

For method 3 clozapine continuers, days of admission were significantly higher before starting clozapine (Mdn = 41.24) than after starting clozapine (Mdn = 8.65), T = 1577, $p < 0.0005$, $r = 0.16$. However, for clozapine discontinuers, days of admission were not statistically significantly different before starting clozapine (Mdn = 31.44) than after starting clozapine (Mdn = 57.03), T = 190, $p = 0.166$. For clozapine continuers, the number of admissions was also significantly higher before starting clozapine (Mdn = 0.58) than after starting clozapine (Mdn =0.00), T = 1944, $p < 0.0005$, $r = 0.23$. This was also true for those that discontinued clozapine, with the number of admissions being significantly higher before starting clozapine (Mdn = 0.82) than after starting clozapine (Mdn = 0.28), T = 337.5, $p = 0.002$, $r = 0.37$.

For method 4 clozapine continuers, days of admission were significantly higher before starting clozapine (Mdn = 46.61) than after starting clozapine (Mdn = 8.65), T = 1664, $p < 0.0005$, $r = 0.33$. However, for clozapine discontinuers, days of admission were not statistically significantly different before starting clozapine (Mdn = 35.98) than after starting clozapine (Mdn = 57.03), T = 204, $p = 0.262$. For clozapine continuers, the number of admissions was also significantly higher before starting clozapine (Mdn = 0.58) than after starting clozapine (Mdn =0.00), T = 1944, $p < 0.0005$, $r = 0.23$. This was also true for those that discontinued clozapine, with the number of admissions being significantly higher before starting clozapine (Mdn = 0.82) than after starting clozapine (Mdn = 0.28), T = 337.5, $p = 0.002$, $r = 0.37$.

For method 5 clozapine continuers, days of admission were significantly higher before starting clozapine (Mdn = 41.24) than after starting clozapine (Mdn = 11.65), T = 1957, $p < 0.0005$, r = 0.26. However, for clozapine discontinuers, days of admission were not statistically significantly different before starting clozapine (Mdn = 31.44) compared with after starting clozapine (Mdn = 17.87), T = 339, $p = 0.161$. For clozapine continuers, the number of admissions was also significantly higher before starting clozapine (Mdn = 0.58) than after starting clozapine (Mdn =0.00), T = 1944, $p < 0.0005$, $r = 0.23$. This was also true for those that discontinued clozapine, with the number of admissions being significantly higher before

starting clozapine (Mdn = 0.82) than after starting clozapine (Mdn = 0.28), T = 337.5, p = 0.002, r = 0.37.

Overall, for patients that continued clozapine, days of admission per year after starting clozapine were fewer than before starting clozapine, with small to moderate effect sizes depending on the method of data analysis. The number of admissions per year was also decreased after starting clozapine by staying on therapy, with a small effect size. For patients that discontinued clozapine, there was either a small increase or no effect on the number of days spent as an inpatient per year after the start date of the clozapine, depending on how the data was analysed. In common with those that continued clozapine however, those that discontinued also largely experienced fewer admissions per year after the clozapine was started, with a moderate effect size and some dependence on the method of data analysis.

5.3.5 Linear regression

As discussed in chapter 2, linear regression allows for a single outcome to be predicted from a single predictor variable. In this context, I have used it to investigate the relationship between the delay to clozapine use and the change in time spent as an inpatient once clozapine has been started. The null hypothesis is that the length of time it takes for clozapine to be prescribed has no effect on the long term efficacy outcomes, as measured by the change in inpatient admissions. I have completed this analysis for the intent to treat group, and separately for clozapine continuers and discontinuers.

5.3.5.1 Intent to treat group

5.3.5.1.1 Method 1

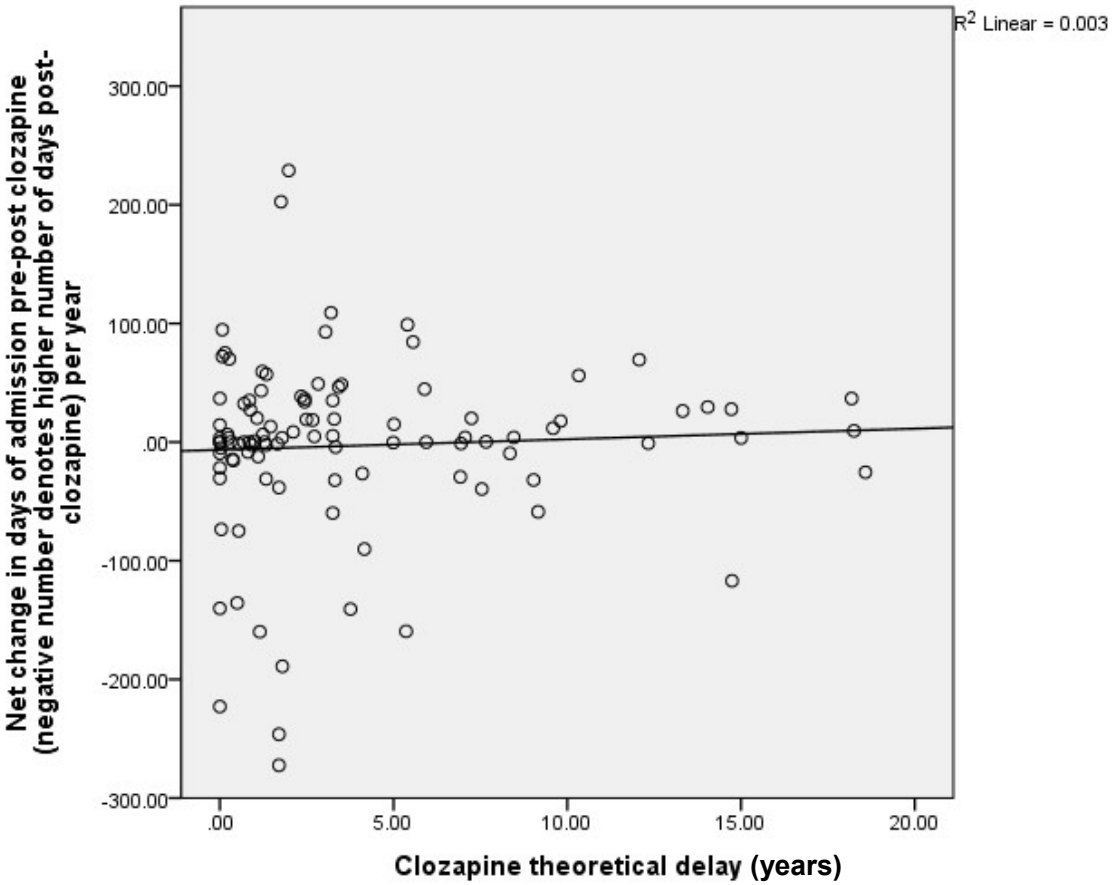

Figure 5-7 Scatter plot for change in days of admission, intent to treat group, method 1

The scatterplot for the data is shown above (Figure 5-7). A positive relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more positive the net change in days of admission per year becomes. Again, a positive net change denotes a lower number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-71). The table shows that the value of *R* is 0.054, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is 0.003, meaning that the clozapine delay accounts for 0.3% of the variation in the change in days of admission. Other variables must therefore account for the remaining 99.7% of the variation in the outcome variable.

Next, I conducted an ANOVA. The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in days of admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-72). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 0.297. This is non-significant at a *p* value of 0.587, and so the regression model does not predict net change in days of admission before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-73). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is -6.487, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is -6.487. This means that 6.487 more days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started, when there is no delay to clozapine use. The gradient of the regression line (b_1) is given in the table as 0.892, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission will increase by 0.892 days. This means that 0.892 fewer days of admission will be spent per year after clozapine initiation. However, this model shows that clozapine delay only accounts for 0.3% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in days of admission per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. Both *t*-tests are non-significant at $p > 0.05$, meaning that the regression coefficients (*b*) are not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-74). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -1.566 and 3.583. Since this interval includes zero, there is no relationship between clozapine theoretical delay and net change in number of days of admission in this population. Additionally, the significance associated with this confidence interval is > 0.05 ($p = 0.466$), demonstrating no statistical significance.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-8).

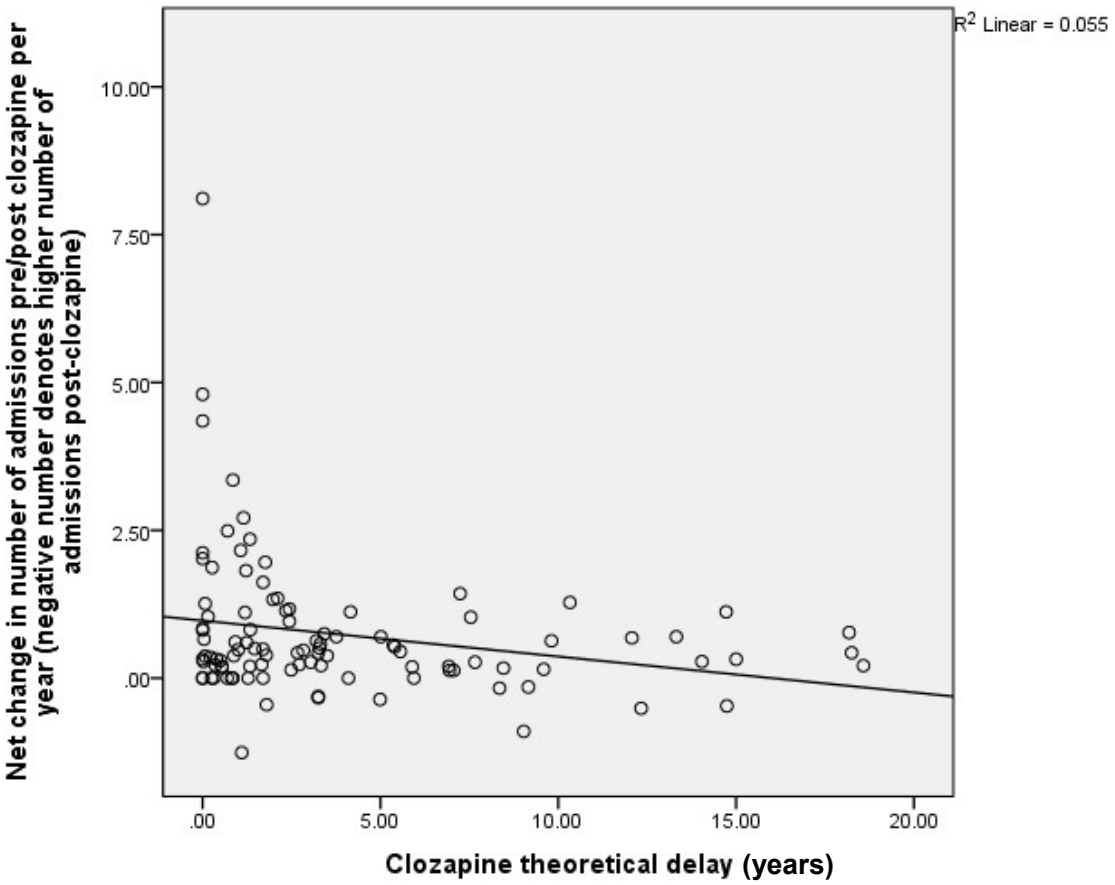

Figure 5-8 Scatterplot for change in number of admissions, intent to treat group, method 1

A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in number of admissions per year becomes.

Again, a negative net change denotes a higher number of admissions after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-75). The table shows that the value of *R* is 0.235, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.055, meaning that the clozapine delay accounts for 5.5% of the variation in the change numbers of admissions. Other variables must therefore account for the remaining 94.5% of the variation in the outcome variable.

Next, I conducted an ANOVA. The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-76). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 5.855. This is significant at a *p* value of 0.017, and so the regression model predicts net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-77). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.973, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.973. This means that a patient has 0.973 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started when the delay to starting clozapine is zero. The gradient of the regression line (b_1) is given in the table as -0.061, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions per year becomes more negative by 0.061 admissions. Therefore 0.061 more admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 5.5% of the

effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. Both *t*-tests are significant at $p < 0.0005$ and $p = 0.017$, meaning that the regression coefficients (*b*) are significantly different to zero, and the theoretical delay to clozapine use does make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-78). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.110 and -0.025. Since this interval does not include zero, there is a negative relationship between clozapine theoretical delay and net change in number of admissions in this population. Additionally, the significance associated with this confidence interval is < 0.05 ($p = 0.02$), demonstrating statistical significance.

5.3.5.1.2 Method 2

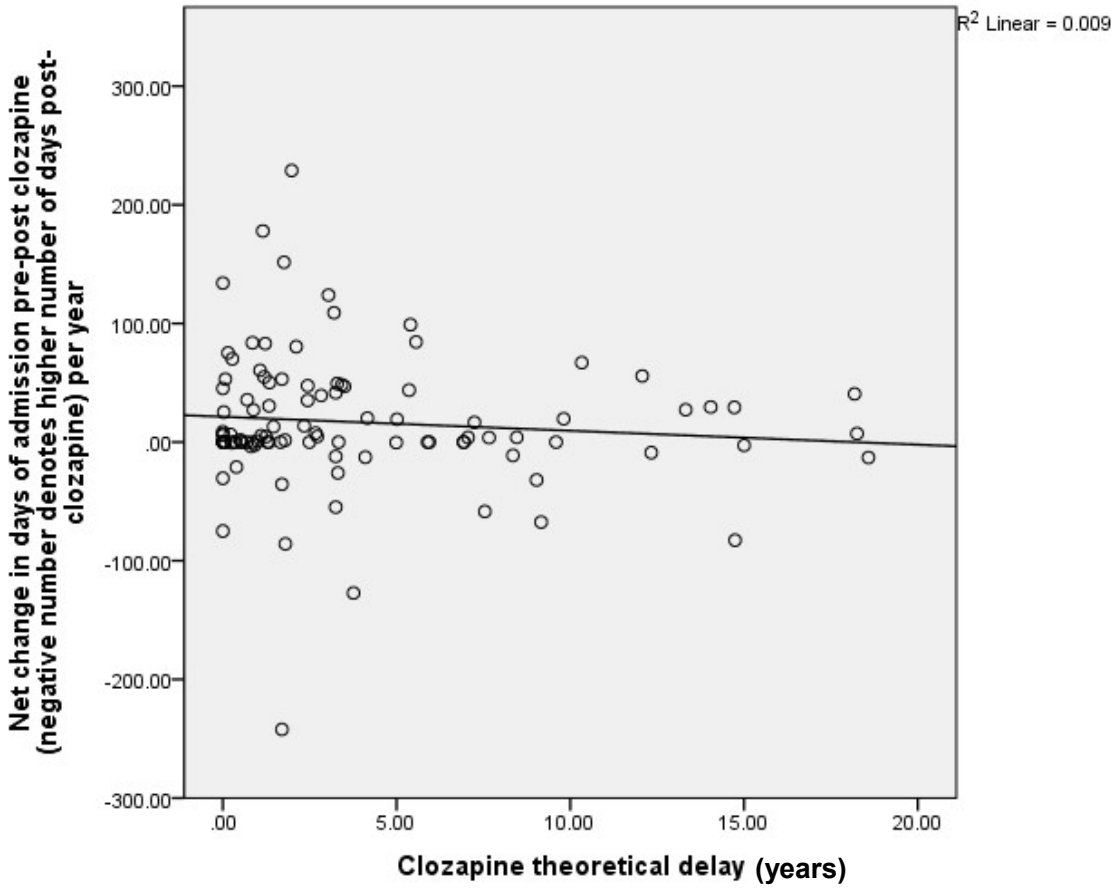

Figure 5-9 Scatterplot for change in days of admission, intent to treat group, method 2

The scatterplot for the data is shown above (Figure 5-9). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in days of admission per year becomes. Again, a negative net change denotes a higher number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-79). The table shows that the value of *R* is 0.95, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is 0.009, meaning that the clozapine delay accounts for 0.9% of the variation in the change in days of admission. Other variables must therefore account for the remaining 99.1% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-80). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 0.901. This is non-significant at a *p* value of 0.345, and so the regression model does not predict net change in days of admission before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-81). The value of b_0 (the constant) is 21.355, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is 21.355. This means that 21.355 fewer days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started when the delay to starting clozapine is zero. The gradient of the regression line (b_1) is given in the table as -1.176, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission per year will become more negative by 1.176 days. Therefore 1.176 more days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 0.9% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in days of admission per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is non-significant at $p > 0.05$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-82) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -3.115 and 0.679. Since this interval includes zero, there is no relationship between clozapine theoretical delay and net change in number of days of admission in this population.

Additionally, the significance associated with this confidence interval is > 0.05 (p = 0.191), demonstrating no statistical significance.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-10). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in number of admissions per year becomes. Again, a negative net change denotes a higher number of admissions after clozapine has started.

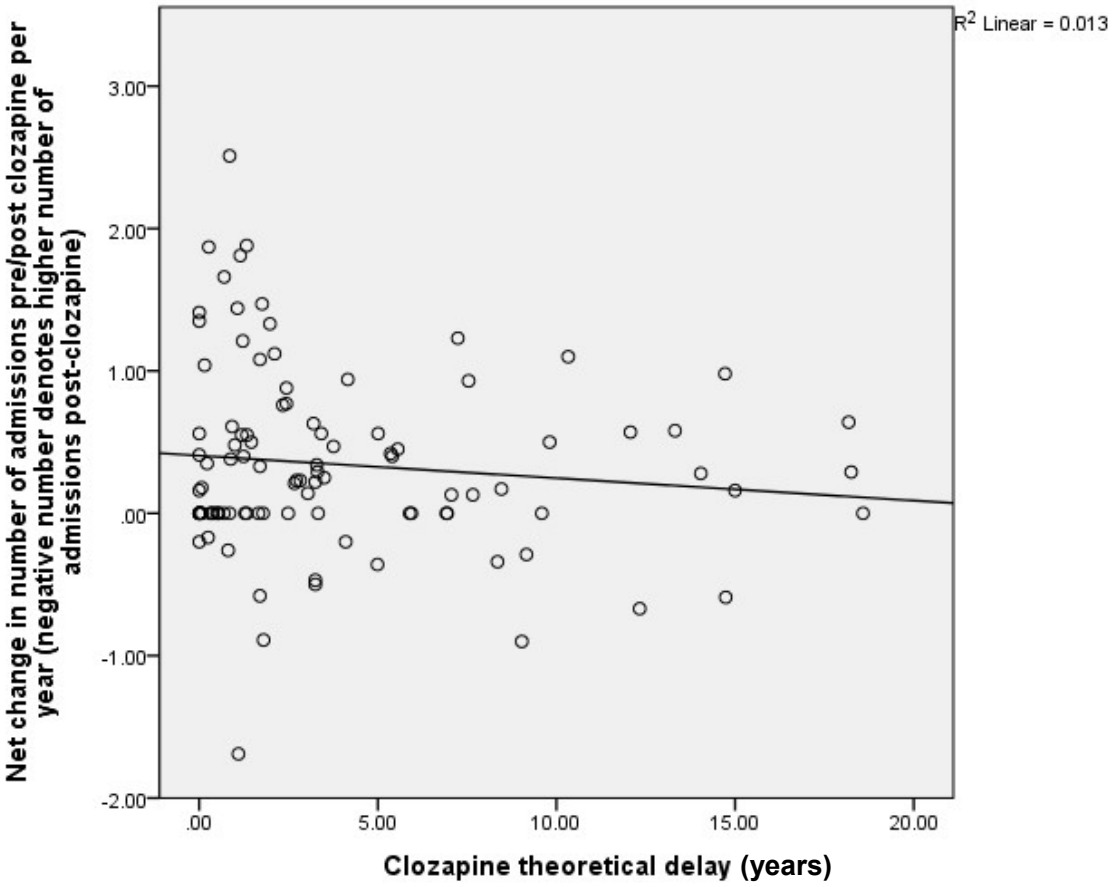

Figure 5-10 Scatterplot for change in number of admissions, intent to treat group, method 2

The summary of the regression model is shown in Appendix G (Table 7-83). The table shows that the value of R is 0.112, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.013, meaning that the

clozapine delay accounts for 1.3% of the variation in the change the numbers of admissions. Other variables must therefore account for the remaining 98.7% of the variation in the outcome variable.

Next, I conducted an ANOVA. The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-84). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 1.275. This is non-significant at a *p* value of 0.261, and so the regression model does not predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-85). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.405, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.405. This means that a patient has 0.405 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started when the delay to starting clozapine is zero. The gradient of the regression line (b_1) is given in the table as -0.016, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions per year will become more negative by 0.016. Therefore 0.016 more admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 1.3% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for clozapine delay is non-significant at $p = 0.261$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the

theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-86). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.040 and 0.007. Since this interval does include zero, there is no relationship between clozapine theoretical delay and net change in number of admissions in this population. Additionally, the significance associated with this confidence interval is $p = 0.203$, demonstrating no statistical significance.

5.3.5.1.3 Method 3

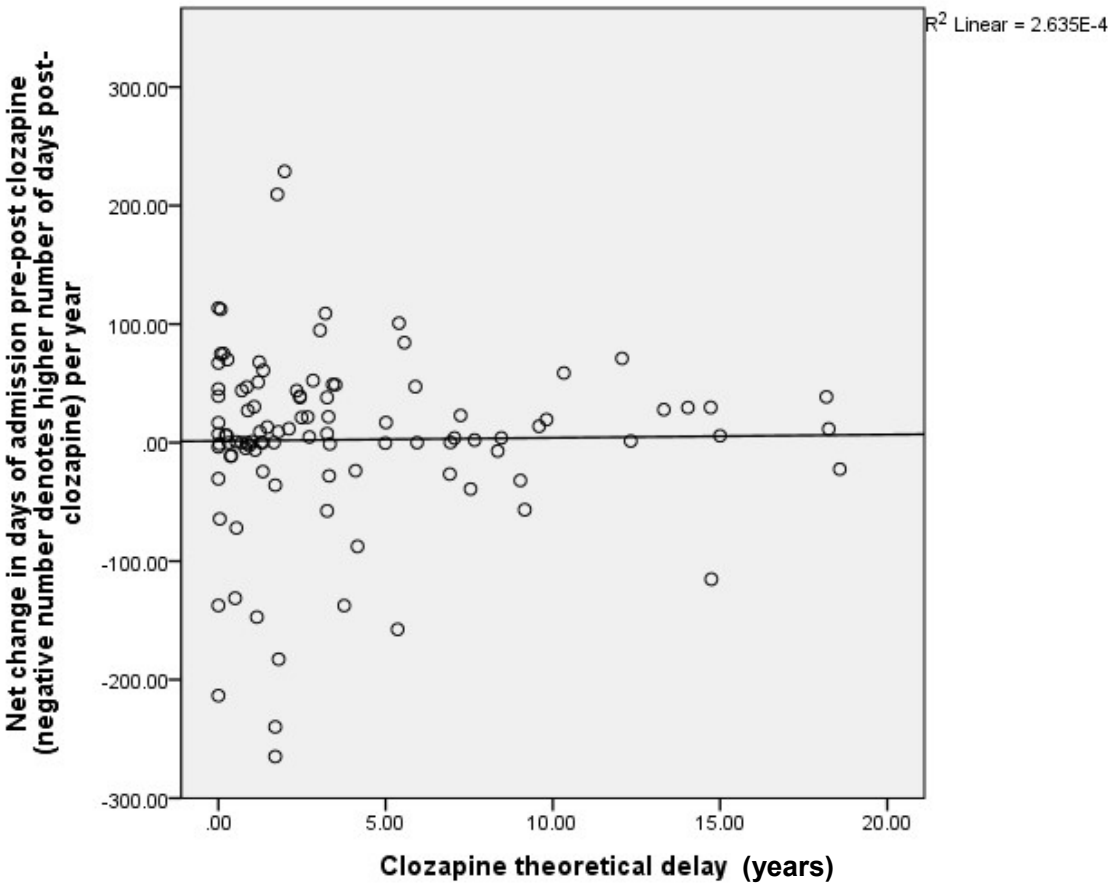

Figure 5-11 Scatterplot for change in days of admission, intent to treat group, method 3

The scatterplot for the data is shown above (Figure 5-11). A positive relationship is seen in

the data, whereby the longer the delay in clozapine prescribing, the more positive the net change in days of admission per year becomes. Again, a positive net change denotes a lower number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-87). The table shows that the value of *R* is 0.16, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is < 0.0005, meaning that the clozapine delay accounts for less than 0.05% of the variation in the change in days of admission. Other variables must therefore account for the remaining 99.95% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-88). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 0.026. This is non-significant at a *p* value of 0.871, and so the regression model does not predict net change in days of admission before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-89). The value of b_0 (the constant) is 1.370, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in days of admission per year is 1.370. This means that 1.370 fewer days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as 0.268, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that 0.268 fewer days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay accounts for less than 0.05% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the

results of which are shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is non-significant at $p > 0.05$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-90) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between –2.291 and 2.835. Since this interval includes zero, there is no relationship between clozapine theoretical delay and net change in number of days of admission in this population. Additionally, the significance associated with this confidence interval is > 0.05 ($p = 0.17$), demonstrating no statistical significance.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-12). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in number of admissions per year becomes. Again, a negative net change denotes a higher number of admissions after clozapine has started.

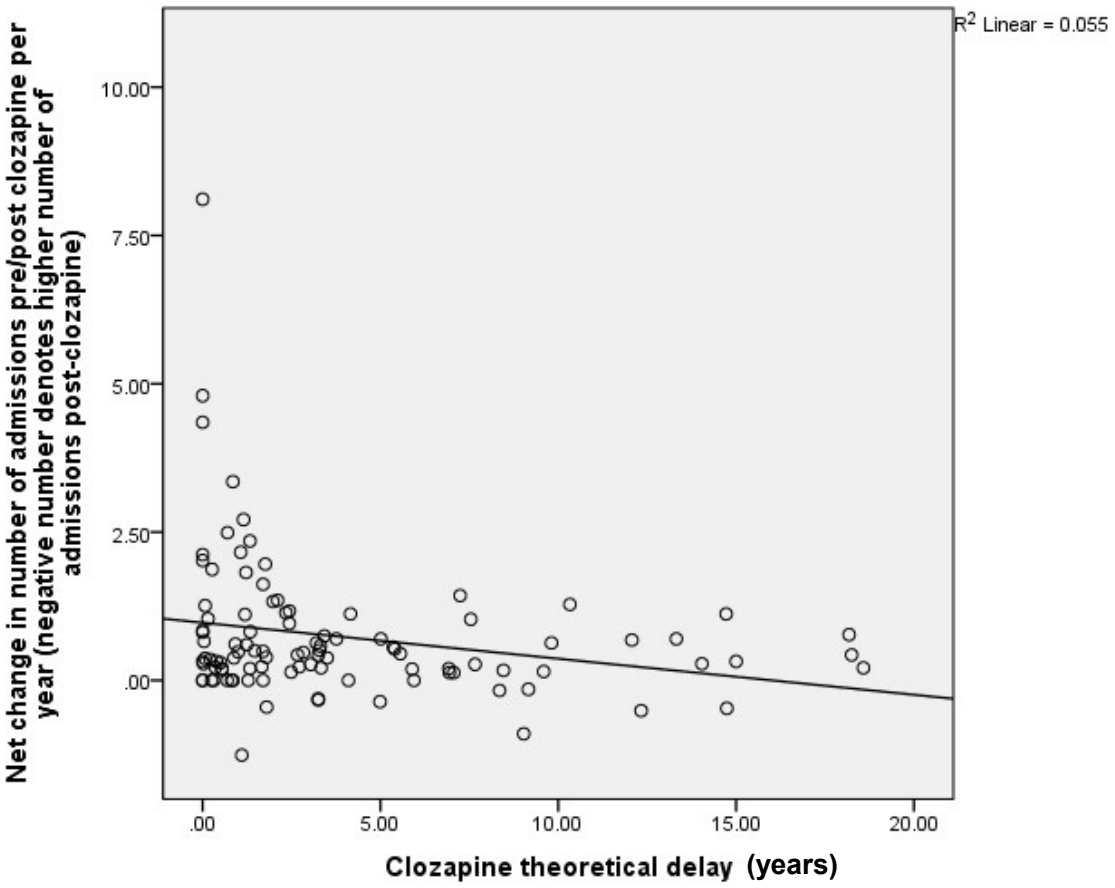

Figure 5-12 Scatterplot for change in number of admissions, intent to treat group, method 3

The summary of the regression model is shown in Appendix G (Table 7-91). The table shows that the value of *R* is 0.235, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.055, meaning that the clozapine delay accounts for 5.5% of the variation in the change numbers of admissions. Other variables must therefore account for the remaining 94.5% of the variation in the outcome variable.

Next, I conducted an ANOVA. The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-92). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 5.855.

This is significant at a *p* value of 0.017, and so the regression model does predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-93). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.973, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.973. This means that a patient has 0.973 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as -0.061, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions will become more negative by 0.061 admissions per year. Therefore, 0.061 more admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 5.5% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for clozapine delay is significant at $p = 0.017$, meaning that the regression coefficient (*b*) is significantly different to zero, and the theoretical delay to clozapine use does make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-94). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.116 and -0.021. Since this interval does not include zero, there is a relationship between clozapine theoretical delay and net change

in number of admissions in this population. Additionally, the significance associated with this confidence interval is $p = 0.027$, demonstrating statistical significance.

5.3.5.1.4 Method 4

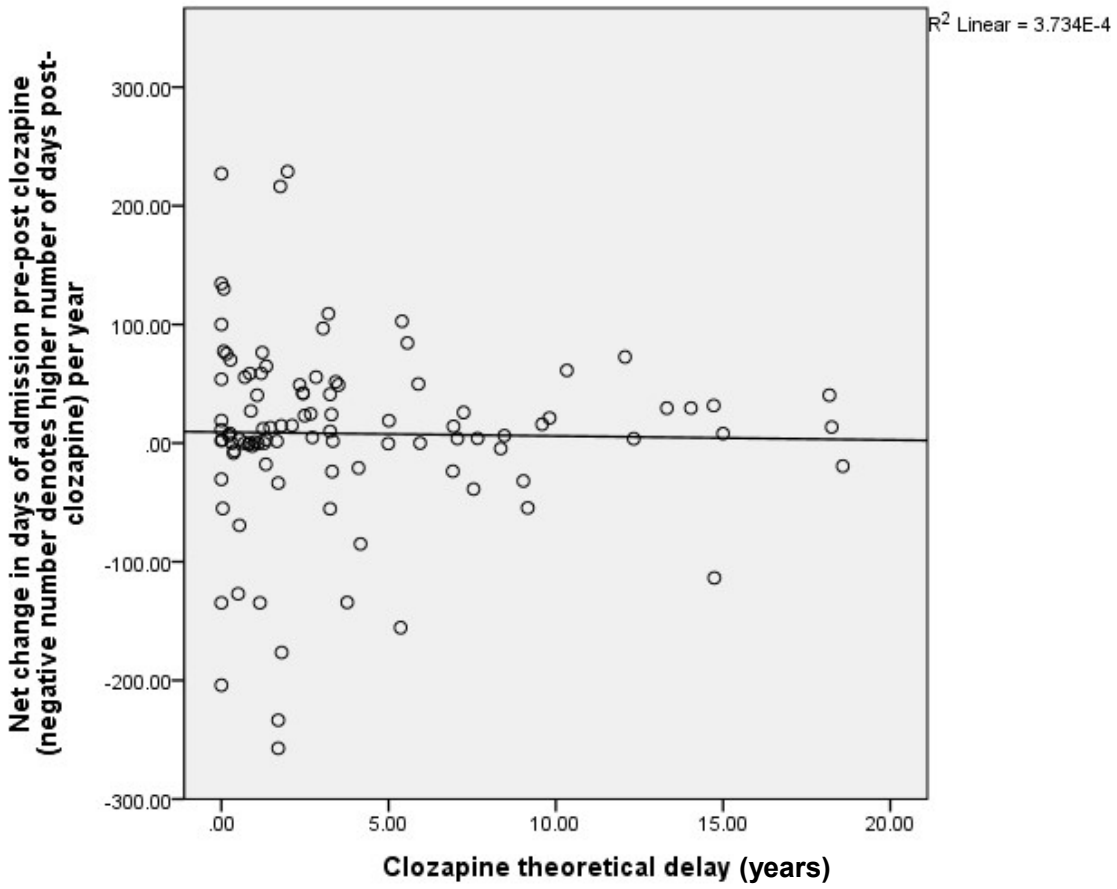

Figure 5-13 Scatterplot for change in days of admission, intent to treat group, method 4

The scatterplot for the data is shown above (Figure 5-13). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in days of admission per year becomes. Again, a negative net change denotes a higher number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-95). The table shows that the value of *R* is 0.19, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is < 0.0005, meaning that the clozapine delay accounts for less than 0.05% of the variation in the change in days of

admission. Other variables must therefore account for the remaining 99.95% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-96). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 0.037. This is non-significant at a *p* value of 0.847, and so the regression model does not predict net change in days of admission before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-97). The value of b_0 (the constant) is 9.284, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is 9.284. This means that 9.284 fewer days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as - 0.333, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission becomes more negative by 0.333 days per year. Therefore 0.333 extra days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay accounts for less than 0.05% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in days of admission per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is non-significant at $p > 0.05$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-98) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between –3.028 and

2.254. Since this interval includes zero, there is no relationship between clozapine theoretical delay and net change in number of days of admission in this population. Additionally, the significance associated with this confidence interval is > 0.05 (p = 0.820), demonstrating no statistical significance.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-14). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in number of admissions per year becomes. Again, a negative net change denotes a higher number of admissions after clozapine has started.

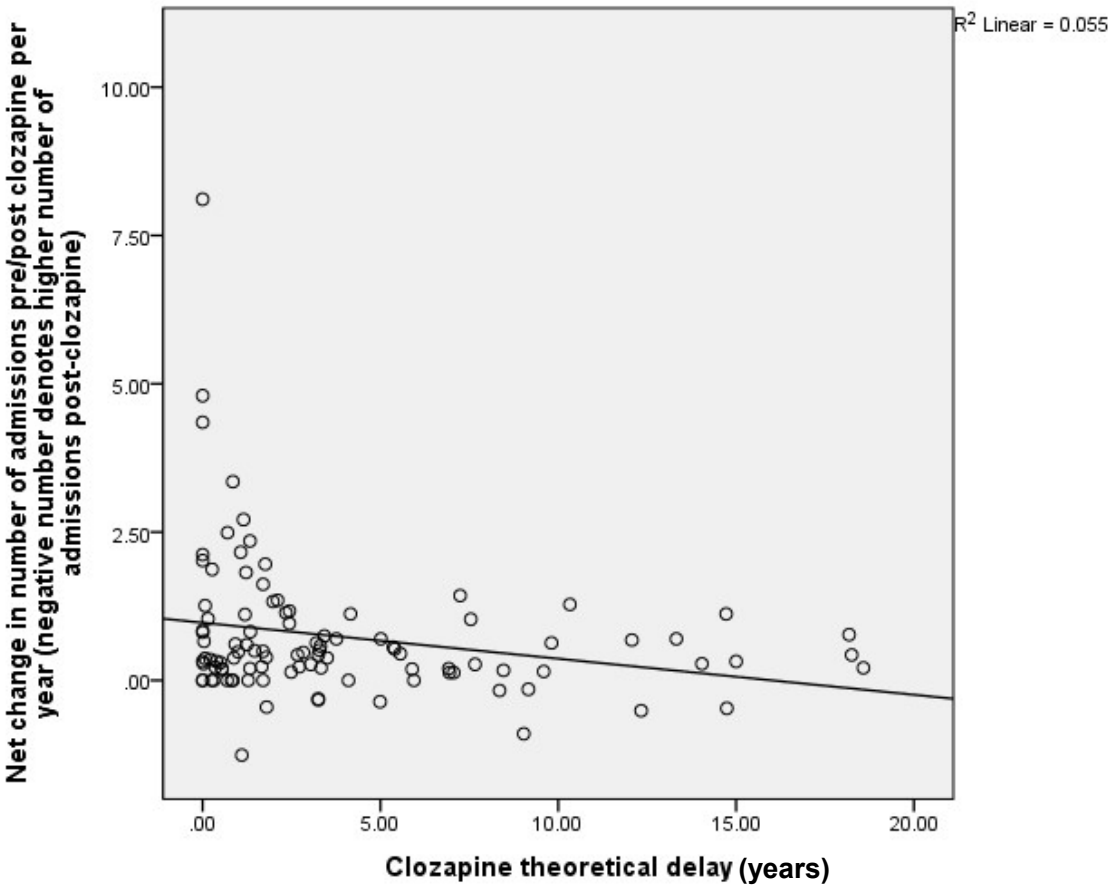

Figure 5-14 Scatterplot for change in number of admissions, intent to treat group, method 4

The summary of the regression model is shown in Appendix G (Table 7-99). The table shows that the value of R is 0.235, and since there is only one predictor variable (clozapine delay),

this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.055, meaning that the clozapine delay accounts for 5.5% of the variation in the change numbers of admissions. Other variables must therefore account for the remaining 94.5% of the variation in the outcome variable.

Next, I conducted an analysis of variance (ANOVA). The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-100). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 5.855. This is significant at a *p* value of 0.017, and so the regression model does predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-101). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.973, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.973. This means that a patient has 0.973 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as -0.061, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions will become more negative by 0.061 per year. Therefore 0.061 more admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 5.5% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is

tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for clozapine delay is significant at $p = 0.017$, meaning that the regression coefficient (*b*) is significantly different to zero, and the theoretical delay to clozapine use does make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-102). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.117 and -0.018. Since this interval does not include zero, there is a relationship between clozapine theoretical delay and net change in number of admissions in this population. Additionally, the significance associated with this confidence interval is $p = 0.025$, demonstrating statistical significance.

5.3.5.1.5 Method 5

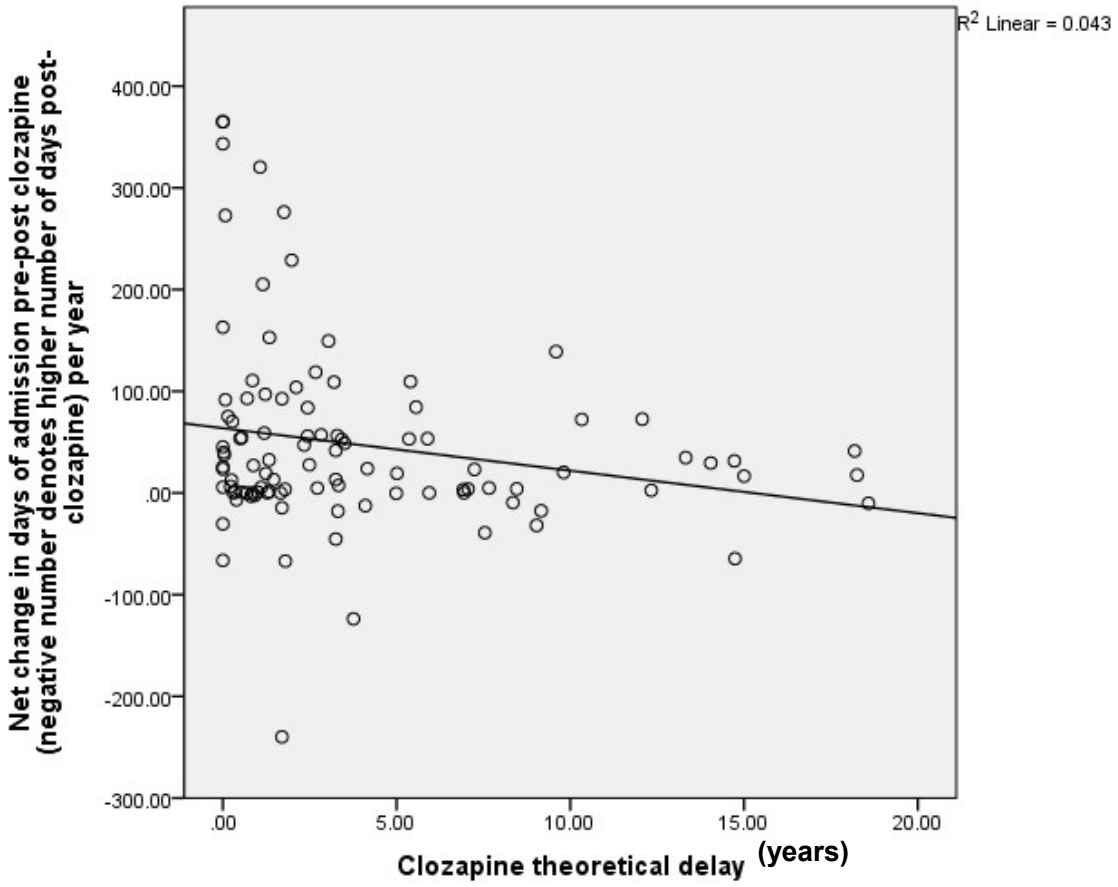

Figure 5-15 Scatterplot for change in days of admission, intent to treat group, method 5

The scatterplot for the data is shown above (Figure 5-15). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in days of admission per year becomes. Again, a negative net change denotes a higher number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-103). The table shows that the value of *R* is 0.208, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is 0.043, meaning that the clozapine delay accounts for 4.3% of the variation in the change in days of admission. Other variables must therefore account for the remaining 95.7% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-104). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 4.502. This is significant at a *p* value of 0.036, and so the regression model does predict net change in days of admission before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-105). The value of b_0 (the constant) is 63.723, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is 63.723. This means that 63.723 fewer days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as – 4.178, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission will become more negative by 4.178 days per year. Therefore 4.178 more days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay accounts for less than 4.3% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is significant at $p = 0.036$, meaning that the regression coefficient (*b*) is significantly different to zero, and the theoretical delay to clozapine use does make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-106) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -7.459 and -1.210. Since this interval does not include zero, there is a genuine negative relationship between clozapine theoretical delay and net change in number of days of admission in this population. This result is significant at $p = 0.017$.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-16). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in number of admissions per year becomes. Again, a negative net change denotes a higher number of admissions after clozapine has started.

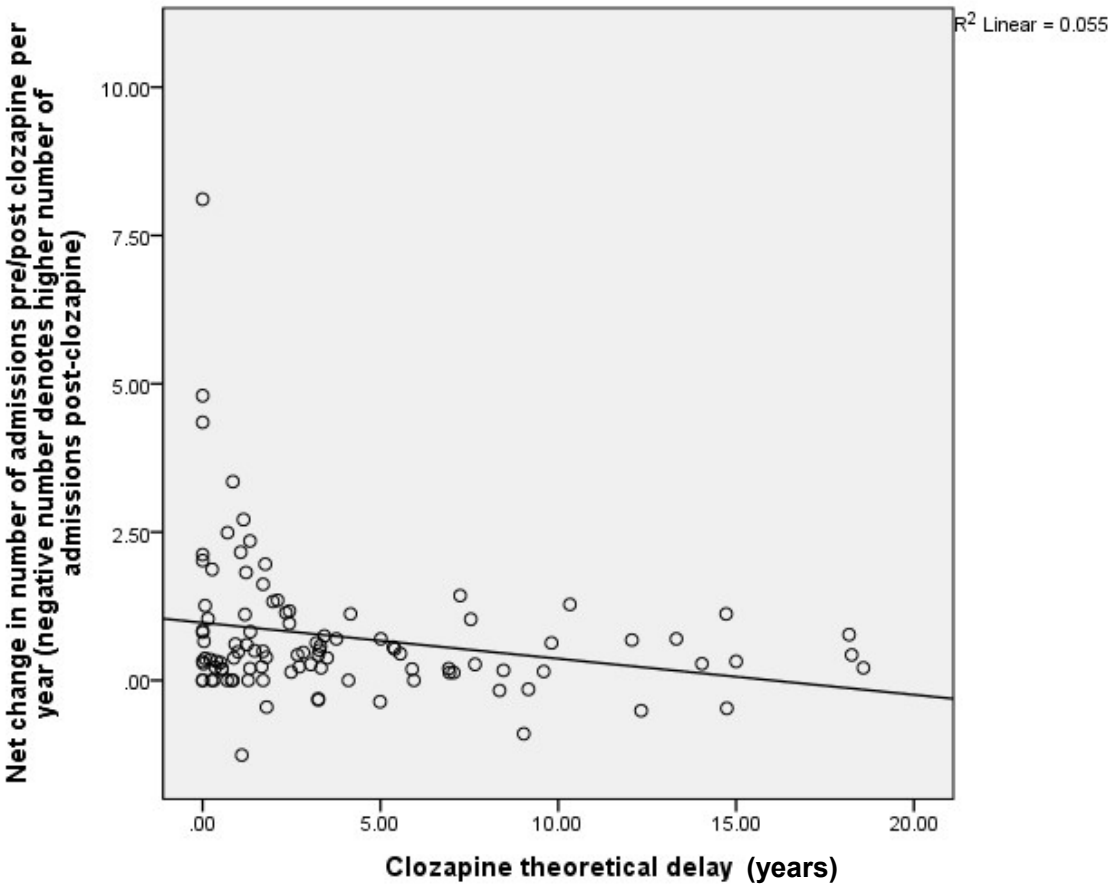

Figure 5-16 Scatterplot for change in number of admissions, intent to treat group, method 5

The summary of the regression model is shown in Appendix G (Table 7-107). The table shows that the value of *R* is 0.235, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.055, meaning that the clozapine delay accounts for 5.5% of the variation in the change numbers of admissions. Other variables must therefore account for the remaining 94.5% of the variation

in the outcome variable.

Next, I conducted an ANOVA. The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-108). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 5.855. This is significant at a *p* value of 0.017, and so the regression model does predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-109). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.973, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.973. This means that a patient has 0.973 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as -0.061, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions will become more negative by 0.061 admissions per year. Therefore 0.061 more admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 5.5% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for clozapine delay is significant at $p = 0.017$, meaning that the regression coefficient (*b*) is significantly different to zero, and the theoretical delay to clozapine use does make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-110). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.113 and -0.023. Since this interval does not include zero, there is a relationship between clozapine theoretical delay and net change in number of admissions in this population. Additionally, the significance associated with this confidence interval is $p = 0.028$, demonstrating statistical significance.

Table 5-24 Intent to treat group linear regression data summary

		Linear regression	ANOVA	Co-efficients		Bootstrapping	Effect of increasing clozapine delay by 1 year
		R^2	F	B_0	B_1		
Method 1	Change in days of admission	0.003	0.297 (p = 0.587)	-6.487	0.892 (p = 0.587)	-1.566 to 3.583 (p = 0.466)	0.892 fewer days of admission per year after clozapine has started
	Change in number of admissions	0.055	5.855 (p = 0.017)*	0.973	-0.061 (p = 0.017)*	-0.110 to -0.025 (p = 0.02)*	0.061 more admissions per year after clozapine has started
Method 2	Change in days of admission	0.009	0.901 (p = 0.345)	21.355	-1.176 (p = 0.345)	-3.115 to 0.679 (p = 0.191)	1.176 more days of admission per year after clozapine has started
	Change in number of admissions	0.013	1.275 (p = 0.261)	0.405	-0.016 (p = 0.261)	-0.040 to 0.007 (p = 0.203)	0.016 more admissions per year after clozapine has started
Method 3	Change in days of admission	<0.0005	0.026 (p = 0.871)	1.370	0.268 (p = 0.871)	–2.291 to 2.835 (p = 0.17)	0.268 fewer days of admission per year after clozapine has started
	Change in number of admissions	0.055	5.855 (p = 0.017)*	0.973	-0.061 (p = 0.017)*	-0.116 to -0.021 (p = 0.027)*	0.061 more admissions per year after clozapine has started
Method 4	Change in days of admission	<0.0005	0.037 (p = 0.847)	9.284	-0.333 (p = 0.847)	–3.028 to 2.254 (p = 0.820)	0.333 more days of admission per year after clozapine has started
	Change in number of admissions	0.055	5.855 (p = 0.017)*	0.973	-0.061 (p = 0.017)*	-0.116 to -0.018 (p = 0.025)*	0.061 more admissions per year after clozapine has started
Method 5	Change in days of admission	0.043	4.502 (p = 0.036)*	63.723	-4.178 (p = 0.036)*	-7.459 to -1.210 (p = 0.017)*	4.178 more days of admission after clozapine has started
	Change in number of admissions	0.055	5.855 (p = 0.017)*	0.973	-0.061 (p = 0.017)*	-0.116 to -0.023 (p = 0.028)*	0.061 more admissions per year after clozapine has started

* reaches statistical significance at p <0.05

The data presented above are summarised in Table 5-24. For all 5 methods of data analysis, clozapine delay predicts less than 6% of the net change in days of admission or number of admissions per year before and after clozapine initiation. The regression models for methods 1, 3, 4 and 5, reached statistical significance for the relationship between clozapine delay and net change in the number of admission pre- and post-clozapine initiation. Only the regression model for method 5 reached statistical significance for the relationship between clozapine delay and the net change in the number of days of admission pre- and post-clozapine. Of the models that reach statistical significance, all predict that an increase in the delay to clozapine use results in more days of admission or total admissions per year once clozapine has been started. An increase in delay to clozapine initiation of one year results in an increase of 4.178 days of admission per year, and 0.061 admissions per year. As the mean theoretical delay to clozapine use for this ITT group was 3.93 years, this results in an average increase of 16.42 days of admission, or 0.24 extra inpatient admissions. All methods of data analysis, with the exception of the change in days of admission for method 1, predict that if clozapine delay is zero, there is a reduction in the number of days spent as an inpatient and the total number of inpatient admissions in the year following clozapine initiation.

5.3.5.2 Clozapine continuers

Next, I repeated the linear regression for the clozapine continuers group.

5.3.5.2.1 Method 1

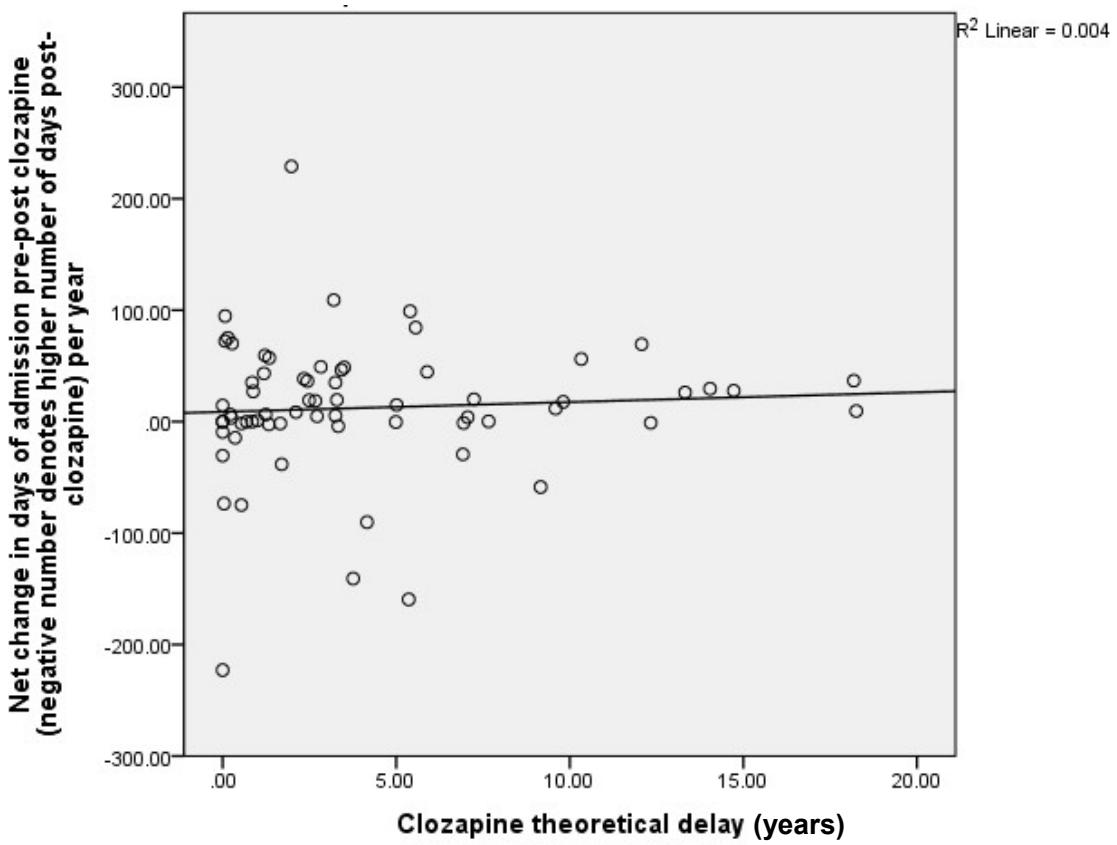

Figure 5-17 Scatterplot for change in days of admission, clozapine continuers, method 1

The scatterplot for the data is shown above (Figure 5-17). A positive relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more positive the net change in days of admission per year becomes. Again, a positive net change denotes a lower number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-111). The table shows that the value of *R* is 0.065, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is 0.004, meaning that the clozapine delay accounts for 0.4% of the variation in the change in days of admission. Other variables must therefore account for the remaining 99.6% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-112). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 0.274. This is non-significant at a *p* value of 0.603, and so the regression model does not predict net change in admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-113). The value of b_0 (the constant) is 8.776, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is 8.776. This means that 8.776 fewer days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as 0.876, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission becomes more positive by 0.876 days per year. Therefore 0.876 fewer days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay accounts for less than 0.05% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is non-significant at $p > 0.05$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-114) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -1.382 and 3.127. Since this interval includes zero, there is no relationship between clozapine theoretical delay and net change in number of days of admission in this population.

Additionally, the significance associated with this confidence interval is > 0.05 (p = 0.443), demonstrating no statistical significance.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-18). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in number of admissions per year becomes. Again, a negative net change denotes a higher number of admissions after clozapine has started.

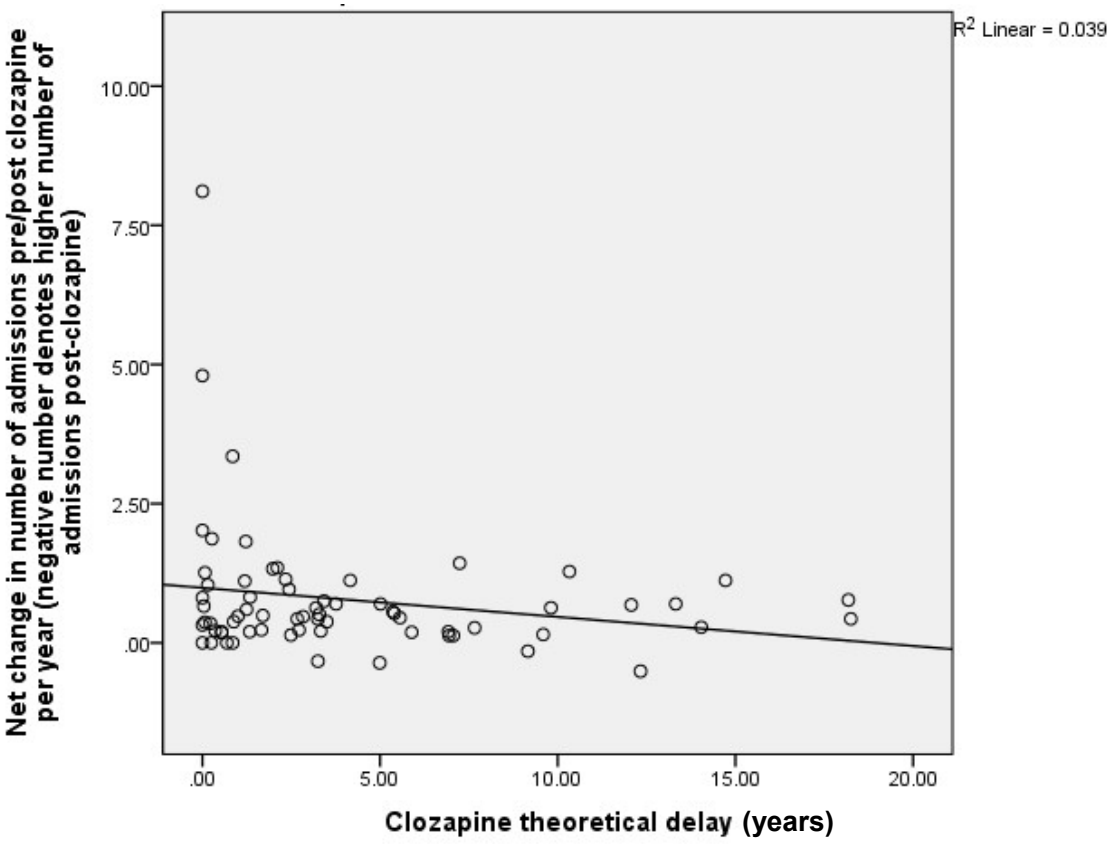

Figure 5-18 Scatterplot for change in number of admissions, clozapine continuers, method 1

The summary of the regression model is shown in Appendix G (Table 7-115). The table shows that the value of R is 0.198, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.039, meaning that the clozapine delay accounts for 3.9% of the variation in the change numbers of

admissions. Other variables must therefore account for the remaining 96.1% of the variation in the outcome variable.

Next, I conducted an ANOVA. The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-116). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 2.645. This is non-significant at a *p* value of 0.109, and so the regression model does not predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-117). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.988, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.988. This means that a patient has 0.988 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as -0.052, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions becomes more negative by 0.052 admissions per year. Therefore 0.052 more admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 3.9% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for clozapine delay is non-significant at $p = 0.109$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the

theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-118). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.126 and -0.004. Since this interval does not include zero, there is a relationship between clozapine theoretical delay and net change in number of admissions in this population. However, the significance associated with this confidence interval is $p = 0.140$, demonstrating no statistical significance.

5.3.5.2.2 Method 2

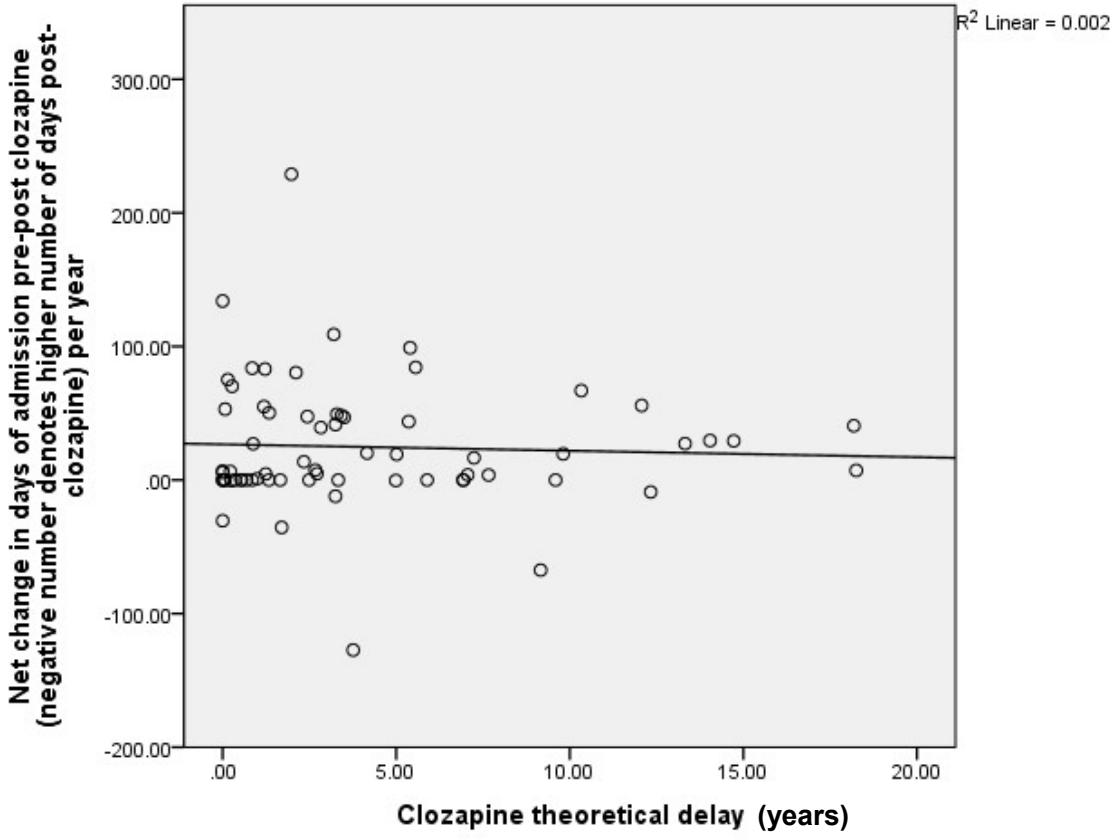

Figure 5-19 Scatterplot for change in days of admission, clozapine continuers, method 2

The scatterplot for the data is shown above (Figure 5-19). A negative relationship is seen in

the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in days of admission per year becomes. Again, a negative net change denotes a higher number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-119). The table shows that the value of *R* is 0.046, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is 0.002, meaning that the clozapine delay accounts for 0.2% of the variation in the change in days of admission. Other variables must therefore account for the remaining 99.8% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-120). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 0.140. This is non-significant at a *p* value of 0.709, and so the regression model does not predict net change in admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-121). The value of b_0 (the constant) is 26.727, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is 26.727. This means that 26.727 fewer days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as - 0.481, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission becomes more negative by 0.481 days per year. Therefore 0.481 more days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay accounts for 0.2% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per

year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is non-significant at $p > 0.05$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-122) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -2.347 and 1.067. Since this interval includes zero, there is no relationship between clozapine theoretical delay and net change in number of days of admission in this population. Additionally, the significance associated with this confidence interval is > 0.05 ($p = 0.590$), demonstrating no statistical significance.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-20). A positive relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more positive the net change in number of admissions per year becomes. Again, a positive net change denotes a lower number of admissions after clozapine has started.

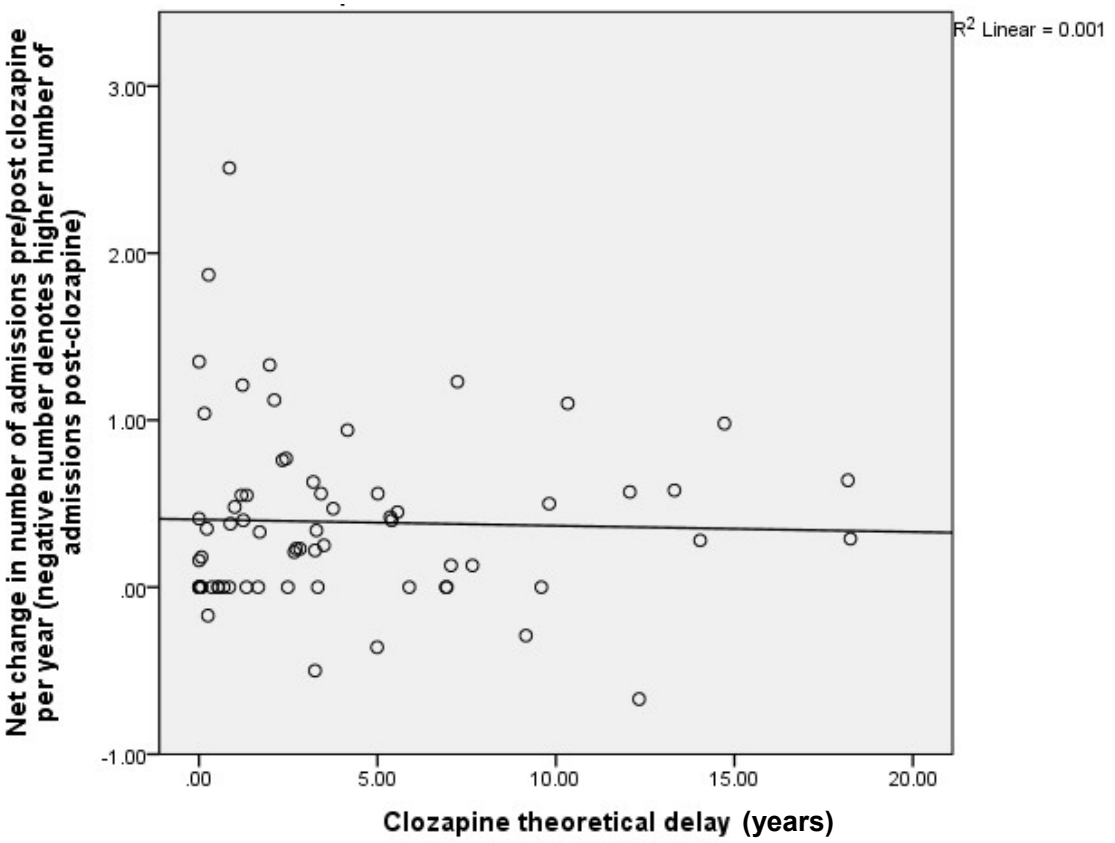

Figure 5-20 Scatterplot for change in number of admissions, clozapine continuers, method 2

The summary of the regression model is shown in Appendix G (Table 7-123). The table shows that the value of *R* is 0.127, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.016, meaning that the clozapine delay accounts for 1.6% of the variation in the change numbers of admissions. Other variables must therefore account for the remaining 98.4% of the variation in the outcome variable.

Next, I conducted an analysis of variance (ANOVA). The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-124). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 1.059. This is non-significant at a *p* value of 0.307, and so the

regression model does not predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-125). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.081, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.081. This means that a patient has 0.081 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as 0.007, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in the number of admissions becomes more positive by 0.007 per year. Therefore 0.007 fewer admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 1.6% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for clozapine delay is non-significant at $p = 0.307$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-126). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.004 and 0.021. Since this interval does include zero, there is no relationship between clozapine theoretical delay and net change in

number of admissions in this population. Additionally, the significance associated with this confidence interval is p = 0.317, demonstrating no statistical significance.

5.3.5.2.3 Method 3

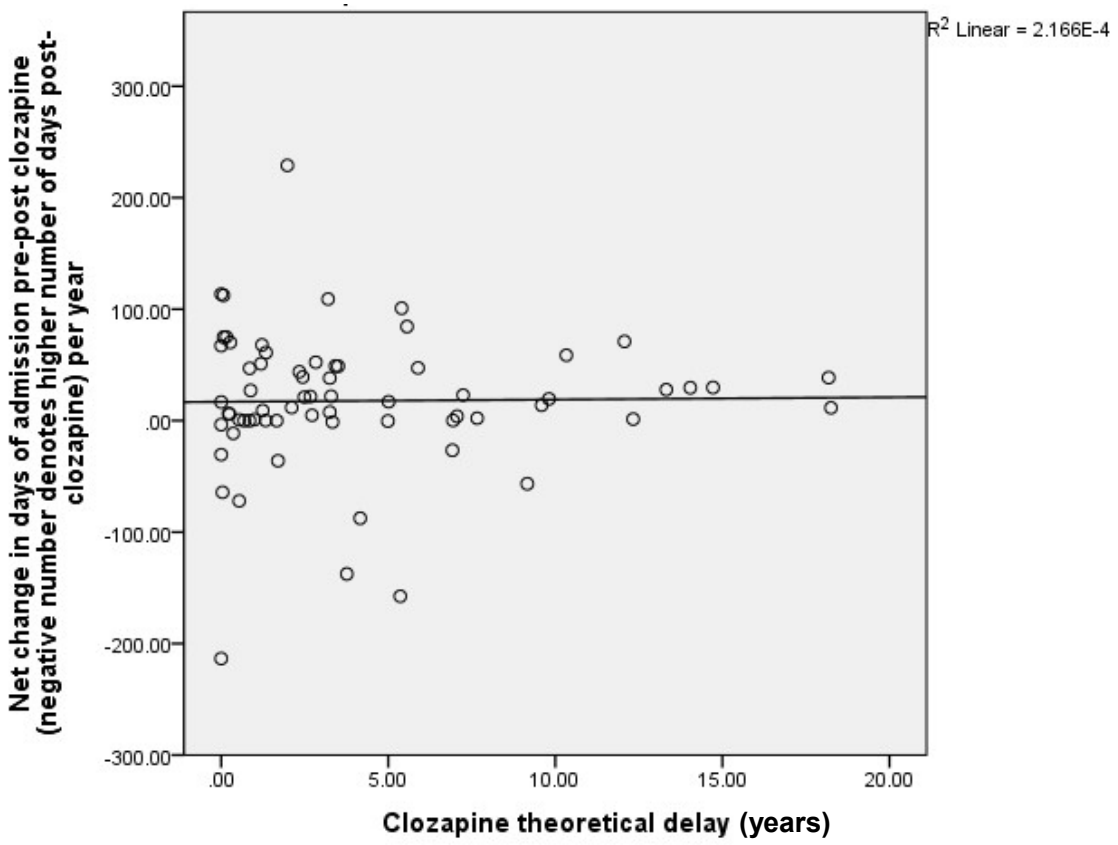

Figure 5-21 Scatterplot for change in days of admission, clozapine continuers, method 3

The scatterplot for the data is shown above (Figure 5-21). A positive relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the less negative the net change in days of admission per year becomes. Again, more positive net change denotes a lower number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-127). The table shows that the value of R is 0.015, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is less than 0.0005, meaning that the clozapine delay accounts for less than 0.05% of the variation in the change

in days of admission. Other variables must therefore account for the remaining 99.95% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-128). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 0.014. This is non-significant at a *p* value of 0.906, and so the regression model does not predict net change in admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-129). The value of b_0 (the constant) is 16.861, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is 16.861. This means that 16.861 fewer days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as 0.203, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission becomes more positive by 0.203 days per year. Therefore 0.203 fewer days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay accounts for less than 0.05% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is non-significant at $p > 0.05$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-130) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -2.349 and 2.469. Since this interval includes zero, there is no relationship between clozapine

theoretical delay and net change in number of days of admission in this population. Additionally, the significance associated with this confidence interval is > 0.05 (p = 0.858), demonstrating no statistical significance.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-22). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in number of admissions per year becomes. Again, a negative net change denotes a higher number of admissions after clozapine has started.

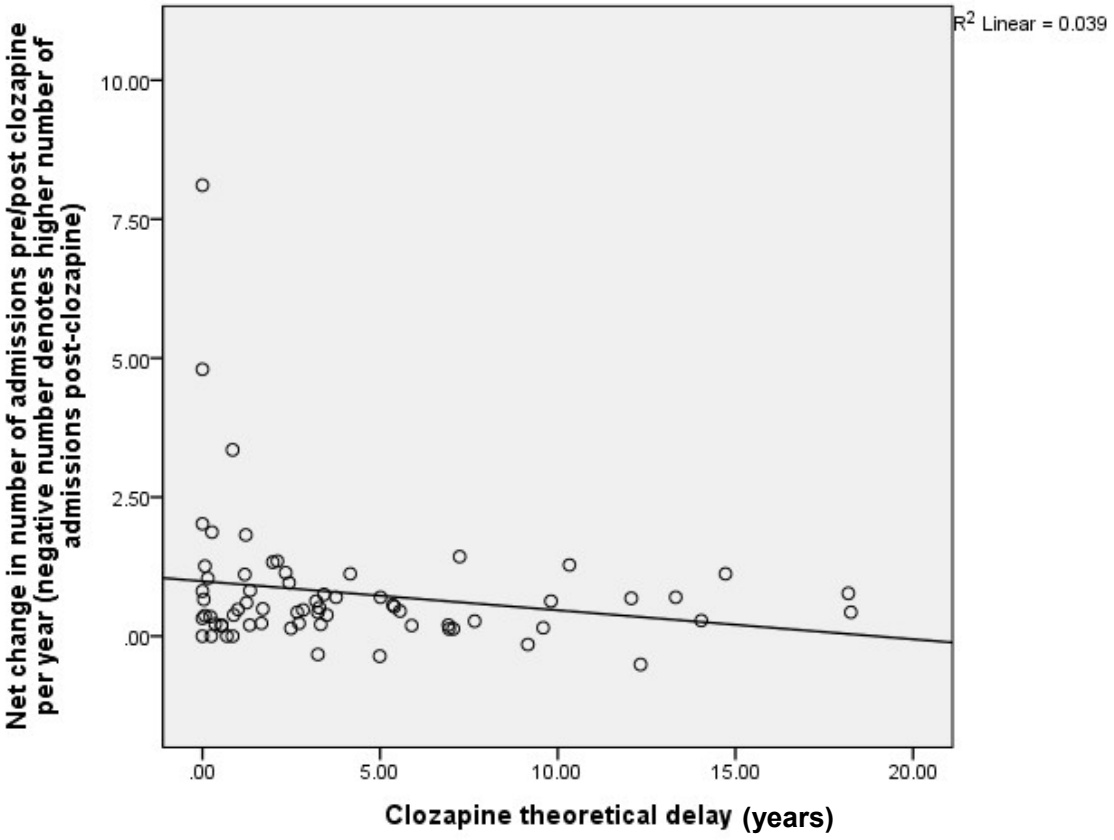

Figure 5-22 Scatterplot for change in number of admissions, clozapine continuers, method 3

The summary of the regression model is shown in Appendix G (Table 7-131). The table shows that the value of R is 0.198, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.039, meaning

that the clozapine delay accounts for 3.9% of the variation in the change numbers of admissions. Other variables must therefore account for the remaining 96.1% of the variation in the outcome variable.

Next, I conducted an ANOVA. The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-132). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 2.645. This is non-significant at a *p* value of 0.109, and so the regression model does not predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-133). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.998, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.998. This means that a patient has 0.998 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as -0.052, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions will become more negative by 0.052 per year. Therefore 0.052 more admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 3.9% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for clozapine delay is non-significant at $p = 0.109$, meaning that the

regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-134). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.129 and -0.005. Since this interval does not include zero, there is a relationship between clozapine theoretical delay and net change in number of admissions in this population. However, the significance associated with this confidence interval is $p = 0.142$, demonstrating no statistical significance.

5.3.5.2.4 Method 4

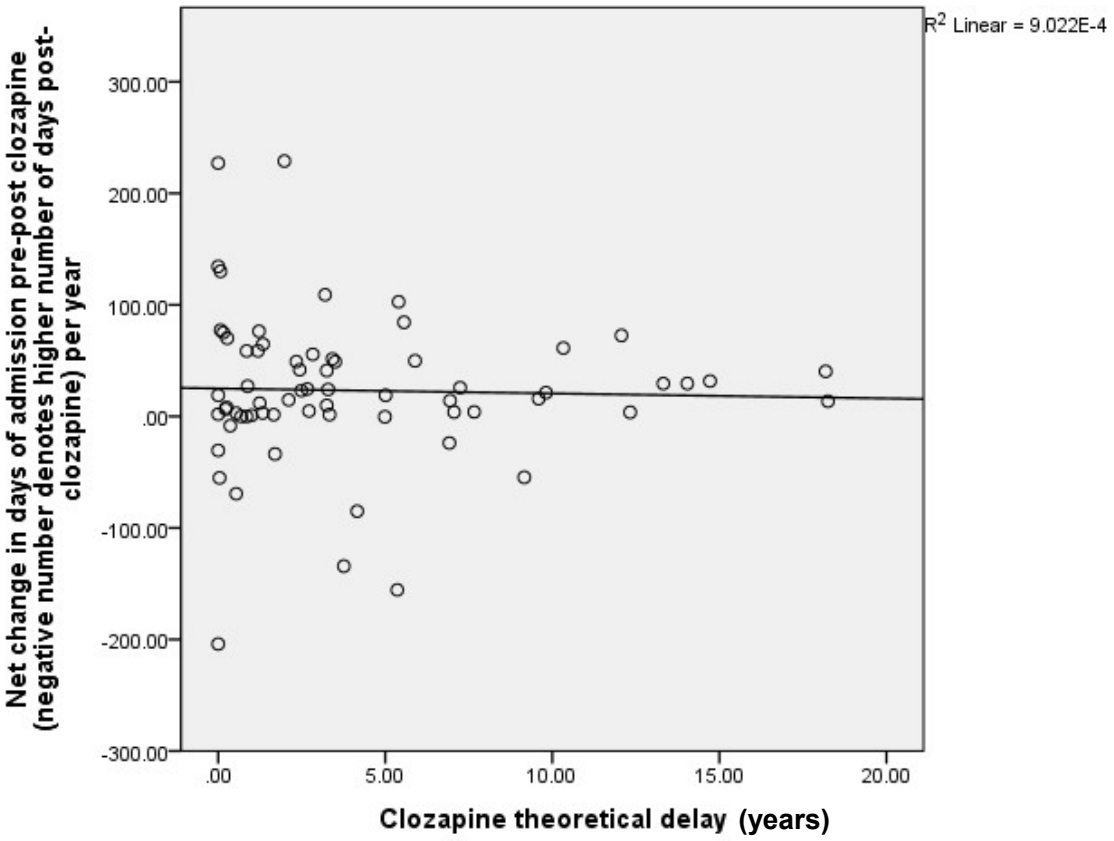

Figure 5-23 Scatterplot for change in days of admission, clozapine continuers, method 4

The scatterplot for the data is shown above (Figure 5-23). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in days of admission per year becomes. Again, a negative net change denotes a higher number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-135). The table shows that the value of *R* is 0.030, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is 0.001, meaning that the clozapine delay accounts for 0.1% of the variation in the change in days of admission. Other variables must therefore account for the remaining 99.9% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-136). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 0.059. This is non-significant at a *p* value of 0.809, and so the regression model does not predict net change in admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-137). The value of b_0 (the constant) is 25.030, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is 25.030. This means that 25.030 fewer days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as - 0.445, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission becomes more negative by 0.445 days per year. Therefore 0.445 more days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay accounts for 0.1% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is non-significant at $p > 0.05$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-138) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -3.181 and 2.220. Since this interval includes zero, there is no relationship between clozapine theoretical delay and net change in number of days of admission in this population.

Additionally, the significance associated with this confidence interval is > 0.05 (p = 0.760), demonstrating no statistical significance.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-24). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in number of admissions per year becomes. Again, a negative net change denotes a higher number of admissions after clozapine has started.

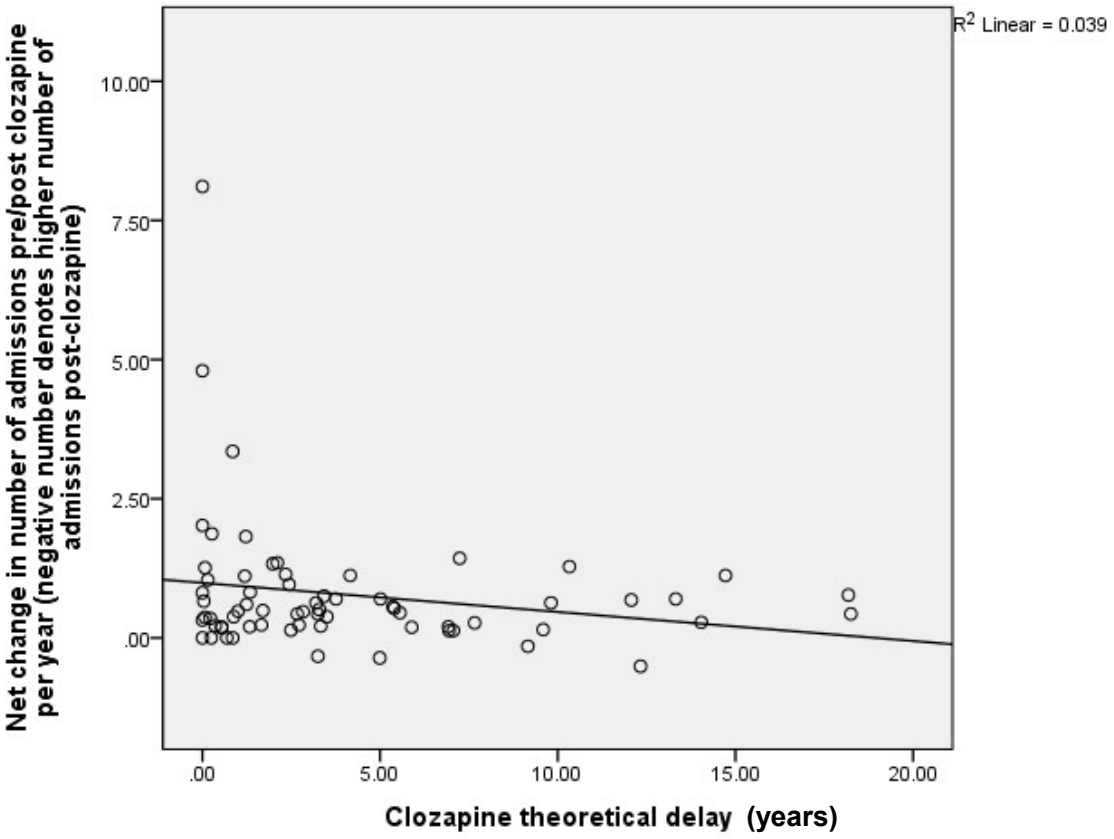

Figure 5-24 Scatterplot for change in number of admissions, clozapine continuers, method 4

The summary of the regression model is shown in Appendix G (Table 7-139). The table shows that the value of R is 0.198, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.039, meaning that the clozapine delay accounts for 3.9% of the variation in the change numbers of

admissions. Other variables must therefore account for the remaining 96.1% of the variation in the outcome variable.

Next, I conducted an ANOVA. The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-140). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 2.645. This is non-significant at a *p* value of 0.109, and so the regression model does not predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-141). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.998, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.998. This means that a patient has 0.998 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as -0.052, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions will become more negative by 0.052 per year. Therefore 0.052 more admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 3.9% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for clozapine delay is non-significant at $p = 0.109$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to

clozapine use does not make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-142). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.127 and -0.005. Since this interval does not include zero, there is a relationship between clozapine theoretical delay and net change in number of admissions in this population. However, the significance associated with this confidence interval is $p = 0.153$, demonstrating no statistical significance.

5.3.5.2.5 Method 5

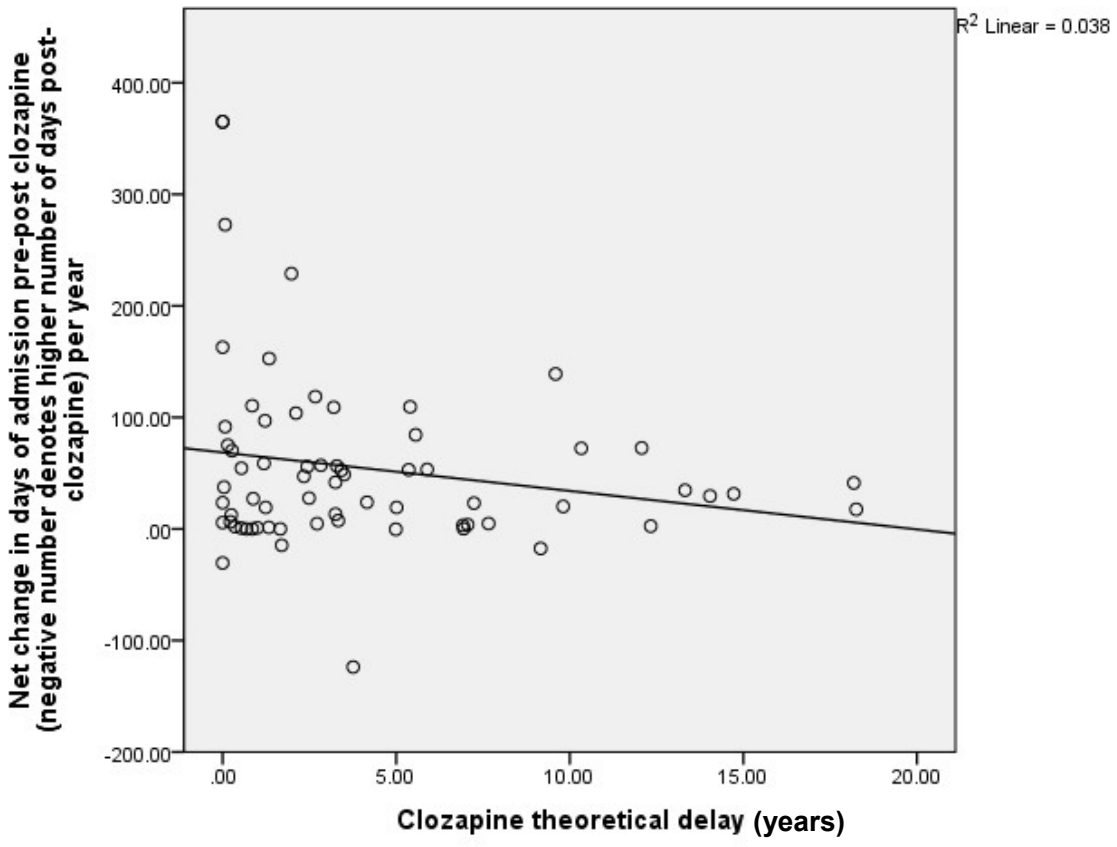

Figure 5-25 Scatterplot for change in days of admission, clozapine continuers, method 5

The scatterplot for the data is shown above (Figure 5-25). A negative relationship is seen in

the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in days of admission per year becomes. Again, a negative net change denotes a higher number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-143). The table shows that the value of *R* is 0.196, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is 0.038, meaning that the clozapine delay accounts for 3.8% of the variation in the change in days of admission. Other variables must therefore account for the remaining 96.2% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-144). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 2.596. This is non-significant at a *p* value of 0.112, and so the regression model does not predict net change in admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-145). The value of b_0 (the constant) is 68.574, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is 68.574. This means that 68.574 fewer days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as – 3.447, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission becomes more negative by 3.447 days per year. Therefore 3.447 more days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay accounts for 3.8% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per

year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is non-significant at $p > 0.05$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-146) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -7.647 and -0.431. Since this interval does not include zero, there is a genuine negative relationship between clozapine theoretical delay and net change in number of days of admission in this population. However, this result is non-significant at $p = 0.079$.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-26). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in number of admissions per year becomes. Again, a negative net change denotes a higher number of admissions after clozapine has started.

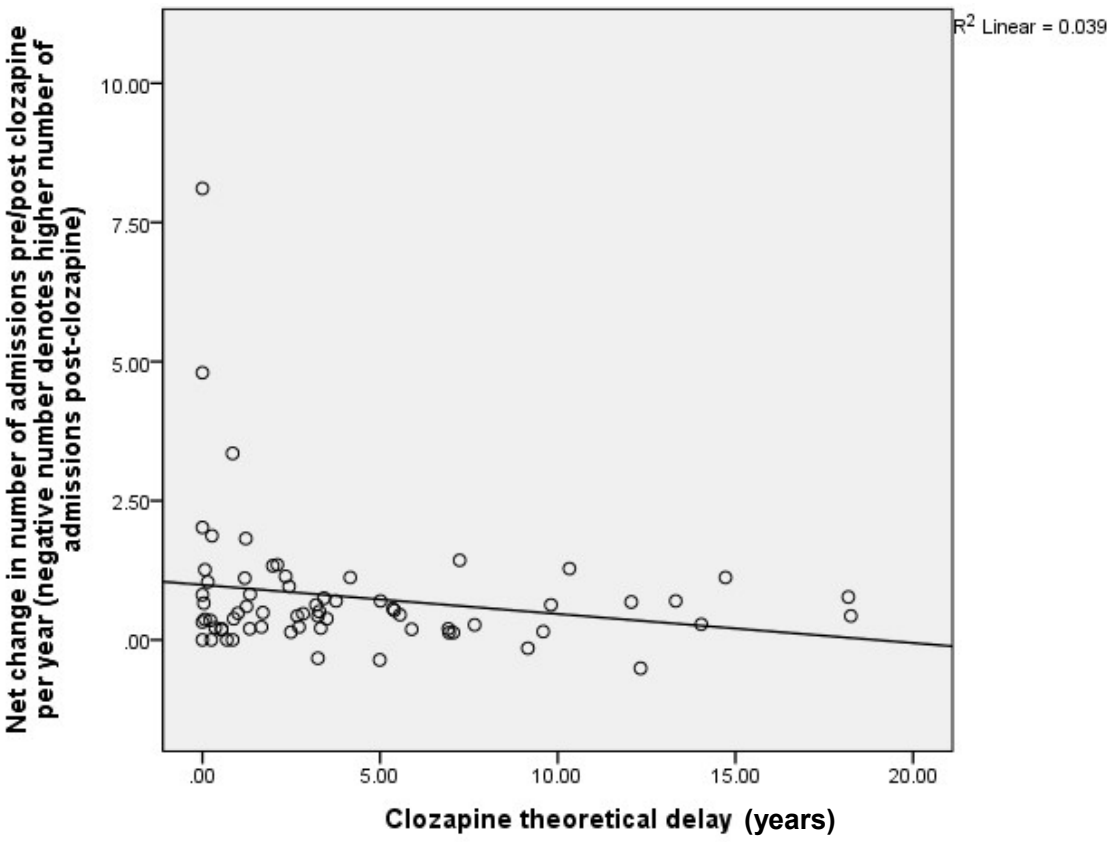

Figure 5-26 Scatterplot for change in number of admissions, clozapine continuers, method 5

The summary of the regression model is shown in Appendix G (Table 7-147). The table shows that the value of *R* is 0.198, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.039, meaning that the clozapine delay accounts for 3.9% of the variation in the change numbers of admissions. Other variables must therefore account for the remaining 96.1% of the variation in the outcome variable.

Next, I conducted an ANOVA. The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-148). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 2.645. This is non-significant at a *p* value of 0.109, and so the regression model does not

predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-149). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.998, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.998. This means that a patient has 0.998 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as -0.052, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions becomes more negative by 0.052 admissions per year. Therefore 0.052 more admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 3.9% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (b), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a t-test, the results of which are shown in the final column of the table. The t-test for clozapine delay is non-significant at $p = 0.109$, meaning that the regression coefficient (b) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-150). The bootstrapped confidence intervals indicate that the population value for b (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.127 and -0.002. Since this interval does not include zero, there is a relationship between clozapine theoretical delay and net change

in number of admissions in this population. However, the significance associated with this confidence interval is $p = 0.153$, demonstrating no statistical significance.

Table 5-25 Clozapine continuers group linear regression data summary

		Linear regression	ANOVA	Co-efficients		Bootstrapping	Effect of increasing delay to clozapine use by 1 year
		R^2	F	B_0	B_1		
Method 1	Change in days of admission	0.004	0.274 (p = 0.603)	8.776	0.876 (p = 0.603)	-1.382 to 3.127 (p = 0.443)	0.876 fewer days of admission per year after clozapine has started
	Change in number of admissions	0.039	2.645 (p = 0.109)	0.988	-0.052 (p = 0.109)	-0.126 to -0.004 (p = 0.140)	0.052 more admissions per year after clozapine has started
Method 2	Change in days of admission	0.002	0.140 (p = 0.709)	26.727	-0.481 (p = 0.709)	-2.347 to 1.067 (p = 0.590)	0.481 more days of admission per year after clozapine has started
	Change in number of admissions	0.016	1.059 (p = 0.307)	0.081	0.007 (p = 0.307)	-0.004 to 0.021 (p = 0.317)	0.007 fewer admissions per year after clozapine has started
Method 3	Change in days of admission	< 0.0005	0.014 (p = 0.906)	16.861	0.203 (p = 0.906)	-2.349 to 2.469 (p = 0.858)	0.203 fewer days of admission per year after clozapine has started
	Change in number of admissions	0.039	2.645 (p = 0.109)	0.988	-0.052 (p = 0.109)	-0.129 to -0.005 (p = 0.142)	0.052 more admissions per year after clozapine has started
Method 4	Change in days of admission	0.001	0.059 (p = 0.809)	25.030	-0.445 (p = 0.809)	-3.181 to 2.220 (p = 0.760)	0.445 more days of admission per year after clozapine has started
	Change in number of admissions	0.039	2.645 (p = 0.109)	0.988	-0.052 (p = 0.109)	-0.127 to -0.005 (p = 0.153)	0.052 more admissions per year after clozapine has started
Method 5	Change in days of admission	0.038	2.596 (p = 0.112)	68.574	-3.447 (p = 0.112)	-7.647 to -0.431 (p = 0.079)	3.447 more days of admission per year after clozapine has started
	Change in number of admissions	0.039	2.645 (p = 0.109)	0.988	-0.052 (p = 0.109)	-0.127 to -0.002 (p = 0.153)	0.052 more admissions per year after clozapine has started

Table 7-25 summarises the data presented above. For all 5 methods of data analysis, clozapine delay predicts less than 4% of the net change in days of admission and number of admissions per year before and after clozapine initiation. None of the models reached statistical significance for the relationship between clozapine delay and net change in days of admission pre- and post-clozapine initiation. All methods of data analysis predict that if clozapine delay is zero, there is a lower number of days of admission and a lower total number of admissions per year once clozapine has been started.

5.3.5.3 Clozapine discontinuers

The linear regression was then repeated for the clozapine discontinuers group.

5.3.5.3.1 Method 1

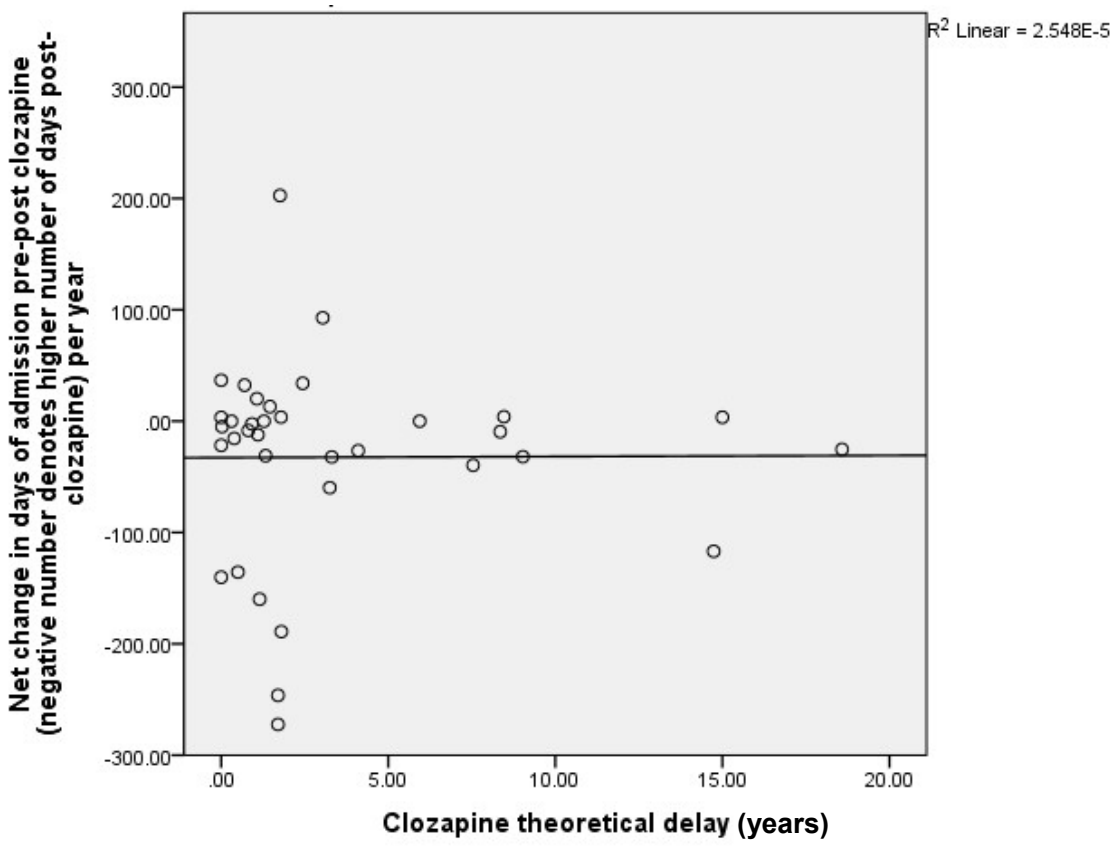

Figure 5-27 Scatterplot for change in days of admission, clozapine discontinuers, method 1

The scatterplot for the data is shown above (Figure 5-27). A positive relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the less negative the net

change in days of admission per year becomes. Again, more positive net change denotes a lower number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-151). The table shows that the value of *R* is 0.005, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is less than 0.0005, meaning that the clozapine delay accounts for less than 0.05% of the variation in the change in days of admission. Other variables must therefore account for the remaining 99.95% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-152). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 0.001. This is non-significant at a *p* value of 0.977, and so the regression model does not predict net change in admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-153). The value of b_0 (the constant) is -32.775, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is -32.775. This means that 32.775 more days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as 0.097, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission will become more positive by 0.097 days per year. Therefore 0.097 fewer days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay accounts for less than 0.05% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-

test, the results of which are shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is non-significant at $p > 0.05$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-154) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -4.642 and 5.594. Since this interval includes zero, there is no relationship between clozapine theoretical delay and net change in number of days of admission in this population. Additionally, the significance associated with this confidence interval is > 0.05 ($p = 0.970$), demonstrating no statistical significance.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-28). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in number of admissions per year becomes. Again, a negative net change denotes a higher number of admissions after clozapine has started.

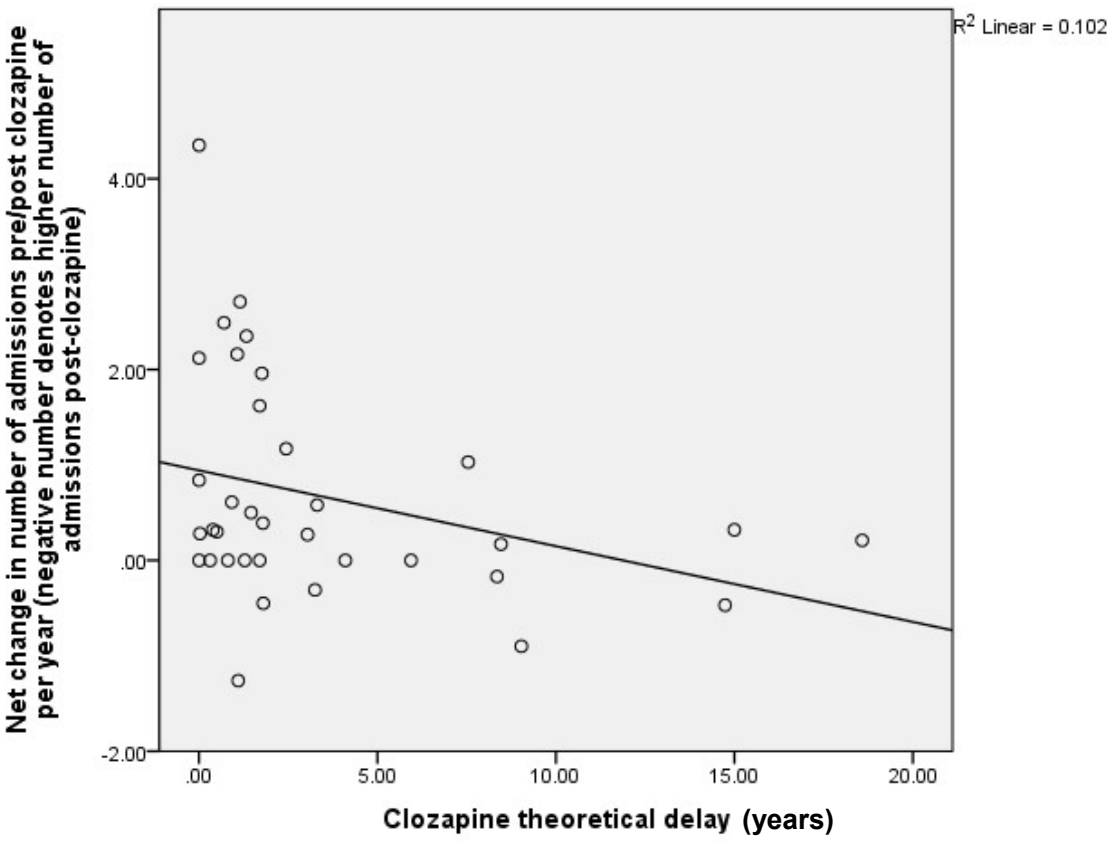

Figure 5-28 Scatterplot for change in number of admissions, clozapine discontinuers, method 1

The summary of the regression model is shown in Appendix G (Table 7-155). The table shows that the value of *R* is 0.320, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.102, meaning that the clozapine delay accounts for 10.2% of the variation in the change numbers of admissions. Other variables must therefore account for the remaining 89.8% of the variation in the outcome variable.

Next, I conducted an analysis of variance (ANOVA). The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-156). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 3.765. This is non-significant at a *p* value of 0.061, and so the

regression model does not predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-157). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.943, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.943. This means that a patient has 0.943 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as -0.079, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions will become more negative by 0.079 admissions per year. Therefore 0.079 more admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 10.2% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for clozapine delay is non-significant at $p = 0.061$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-158). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.170 and -0.031. Since this interval does not include zero, there is a relationship between clozapine theoretical delay and net change

in number of admissions in this population. Additionally, the significance associated with this confidence interval is $p = 0.027$, demonstrating statistical significance.

5.3.5.3.2 Method 2

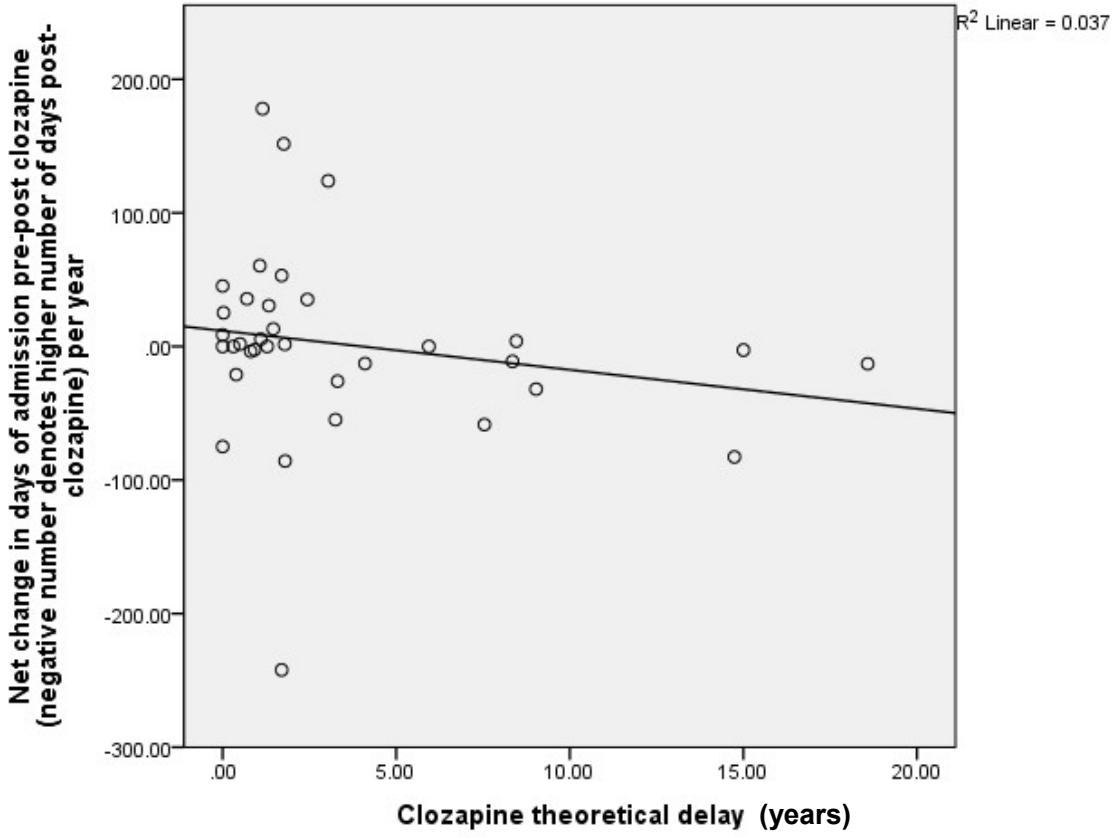

Figure 5-29 Scatterplot for change in days of admission, clozapine discontinuers, method 2

The scatterplot for the data is shown above (Figure 5-29). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in days of admission per year becomes. Again, a negative net change denotes a higher number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-159). The table shows that the value of *R* is 0.193, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is 0.037, meaning that the clozapine delay accounts for 3.7% of the variation in the change in days of admission.

Other variables must therefore account for the remaining 96.3% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-160). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 1.279. This is non-significant at a *p* value of 0.266, and so the regression model does not predict net change in admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-161). The value of b_0 (the constant) is 11.724, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is 11.724. This means that 11.724 fewer days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as – 2.918, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission will become more negative by 2.918 days per year. Therefore 2.918 more days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay accounts for 3.7% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is non-significant at $p > 0.05$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-162) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -6.469 and -0.127. Since this interval does not include zero, there is a genuine negative relationship

between clozapine theoretical delay and net change in number of days of admission in this population. However, this result is non-significant at $p = 0.093$.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-30). A positive relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more positive the net change in number of admissions per year becomes. Again, a positive net change denotes a lower number of admissions after clozapine has started.

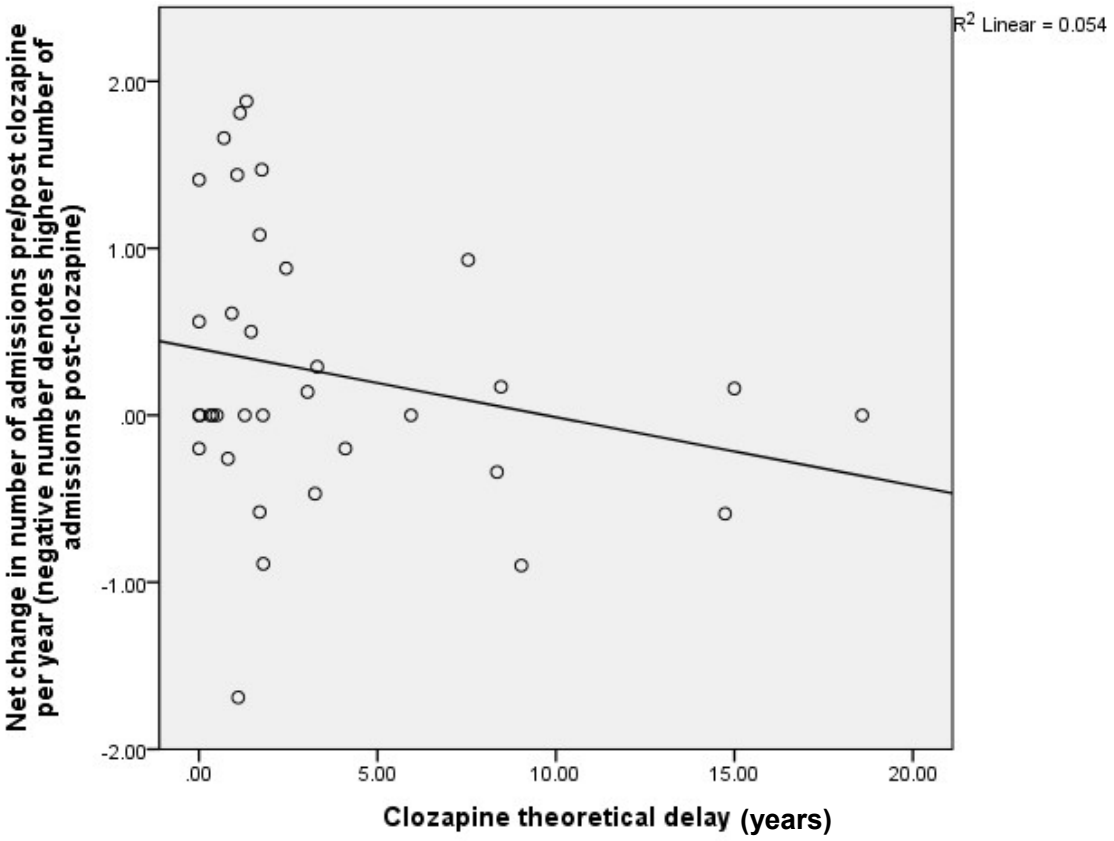

Figure 5-30 Scatterplot for change in number of admissions, clozapine discontinuers, method 2

The summary of the regression model is shown in Appendix G (Table 7-163). The table shows that the value of *R* is 0.136, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.019, meaning that the clozapine delay accounts for 1.9% of the variation in the change numbers of

admissions. Other variables must therefore account for the remaining 98.1% of the variation in the outcome variable.

Next, I conducted an analysis of variance (ANOVA). The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-164). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 0.623. This is non-significant at a *p* value of 0.436, and so the regression model does not predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-165). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.359, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.359. This means that a patient has 0.359 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as 0.015, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions will become more positive by 0.015 admissions per year of extra delay. Therefore 0.015 fewer admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 1.9% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for clozapine delay is non-significant at $p = 0.436$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the

theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-166). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.014 and 0.051. Since this interval does include zero, there is no relationship between clozapine theoretical delay and net change in number of admissions in this population. Additionally, the significance associated with this confidence interval is $p = 0.051$, demonstrating no statistical significance.

5.3.5.3.3 Method 3

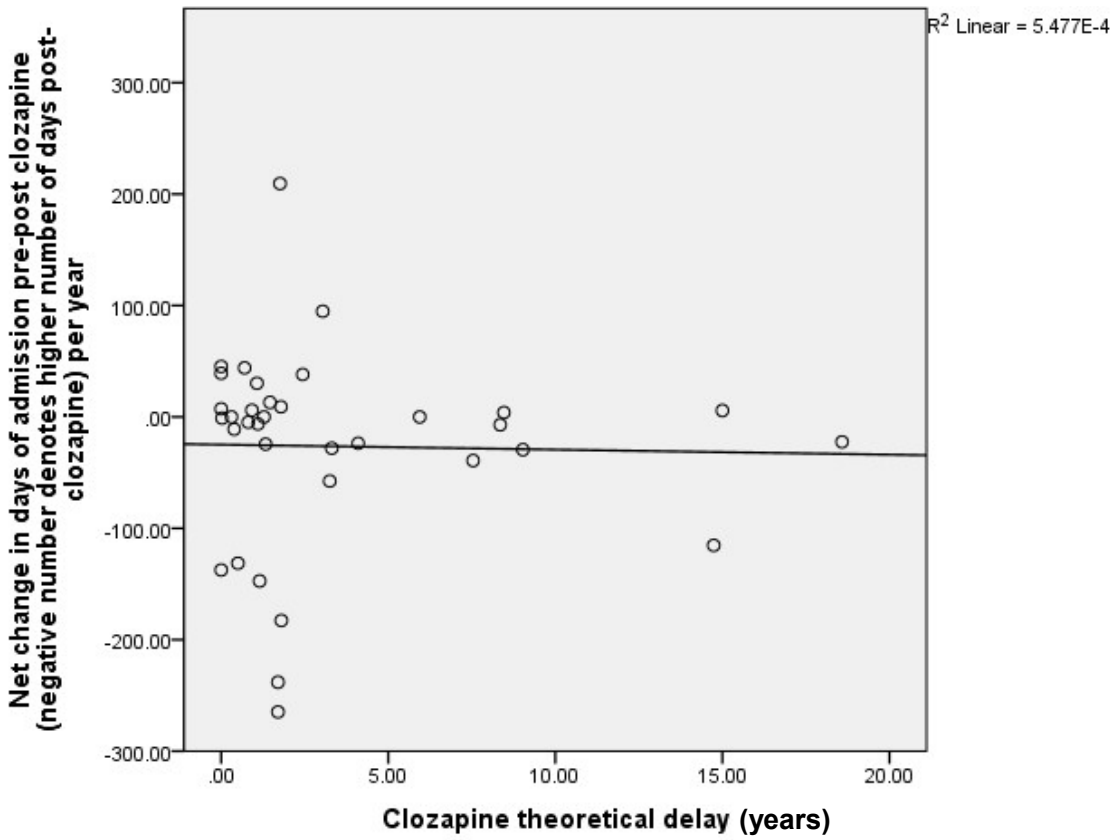

Figure 5-31 Scatterplot for change in days of admission, clozapine discontinuers, method 3

The scatterplot for the data is shown above (Figure 5-31). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net

change in days of admission per year becomes. Again, a negative net change denotes a higher number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-167). The table shows that the value of *R* is 0.023, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is 0.001, meaning that the clozapine delay accounts for 0.1% of the variation in the change in days of admission. Other variables must therefore account for the remaining 99.9% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-168). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 0.017. This is non-significant at a *p* value of 0.898, and so the regression model does not predict net change in admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-169). The value of b_0 (the constant) is -25.284, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is -25.284. This means that 25.284 more days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as -0.435, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission will become more negative by 0.435 per year of extra delay. Therefore 0.435 more days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay accounts for only 0.01% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-

test, the results of which are shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is non-significant at $p > 0.05$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-170) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -5.171 and 4.694. Since this interval includes zero, there is no relationship between clozapine theoretical delay and net change in number of days of admission in this population. Additionally, the significance associated with this confidence interval is > 0.05 ($p = 0.842$), demonstrating no statistical significance.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-32). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in number of admissions per year becomes. Again, a negative net change denotes a higher number of admissions after clozapine has started.

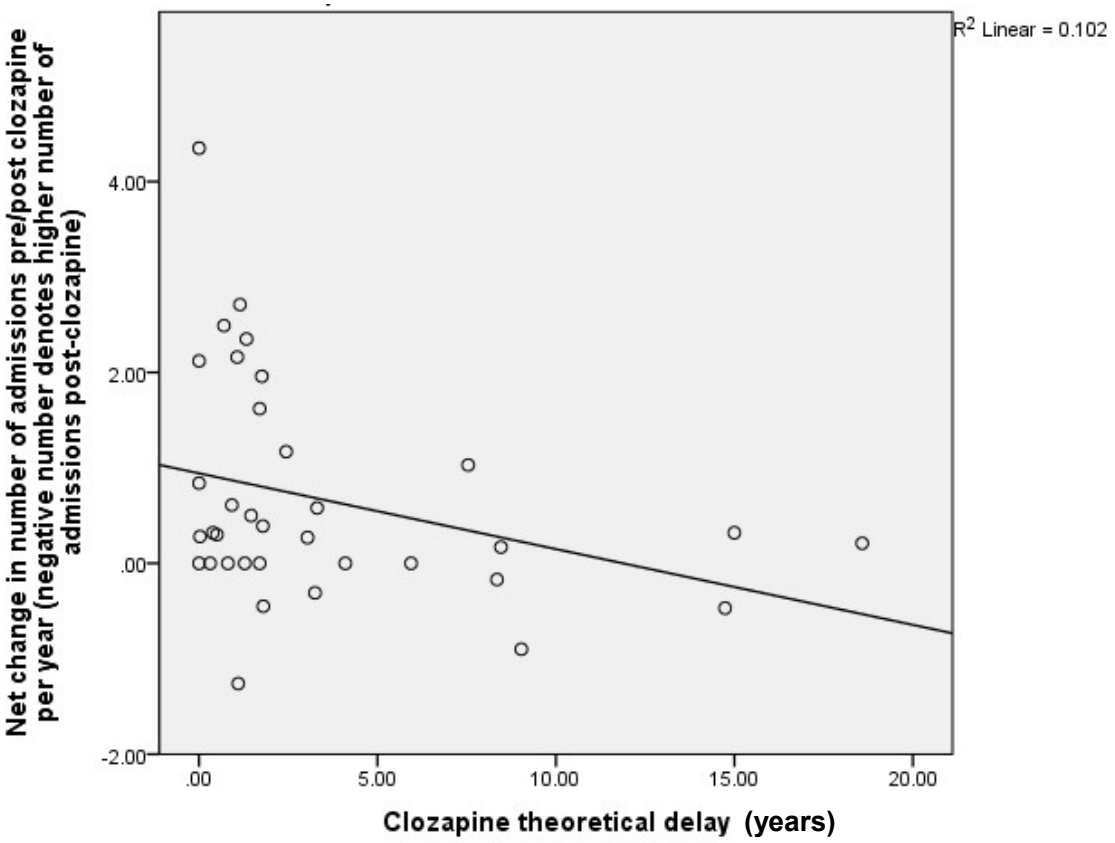

Figure 5-32 Scatterplot for change in number of admissions, clozapine discontinuers, method 3

The summary of the regression model is shown in Appendix G (Table 7-171). The table shows that the value of *R* is 0.320, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.102, meaning that the clozapine delay accounts for 10.2% of the variation in the change numbers of admissions. Other variables must therefore account for the remaining 89.8% of the variation in the outcome variable.

Next, I conducted an analysis of variance (ANOVA). The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-172). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the F-ratio is calculated, and shown as 3.765. This is non-significant at a p value of 0.061, and so the

regression model does not predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-173). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.943, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.943. This means that a patient has 0.943 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as -0.079, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions will become more negative by 0.079 admissions for each extra year of clozapine delay. Therefore 0.079 more admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 10.2% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (b), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for clozapine delay is non-significant at $p = 0.061$, meaning that the regression coefficient (b) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-174). The bootstrapped confidence intervals indicate that the population value for b (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.171 and -0.028. Since this interval does not include zero, there is a relationship between clozapine theoretical delay and net change

in number of admissions in this population. However, the significance associated with this confidence interval is p = 0.026, demonstrating statistical significance.

5.3.5.3.4 Method 4

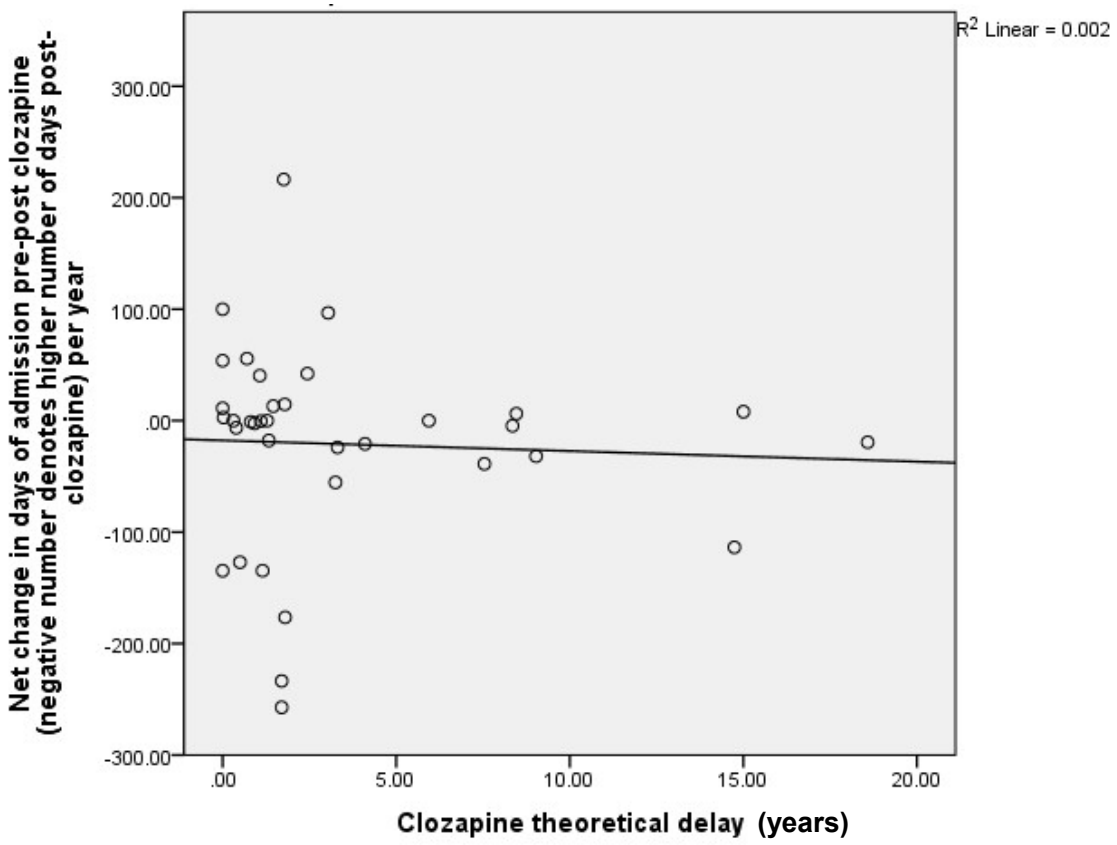

Figure 5-33 Scatterplot for change in days of admission, clozapine discontinuers, method 4

The scatterplot for the data is shown above (Figure 5-33). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in days of admission per year becomes. Again, a negative net change denotes a higher number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-175). The table shows that the value of R is 0.049, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is 0.002, meaning that the clozapine delay accounts for 0.2% of the variation in the change in days of admission.

Other variables must therefore account for the remaining 99.8% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-176). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 0.078. This is non-significant at a *p* value of 0.781, and so the regression model does not predict net change in admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-177). The value of b_0 (the constant) is -17.783, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is -17.783. This means that 17.783 more days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as – 0.951, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission becomes more negative by 0.951 days. Therefore 0.951 more days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay accounts for 0.2% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is non-significant at $p > 0.05$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-178) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -6.453 and 4.577. Since this interval includes zero, there is no relationship between clozapine

theoretical delay and net change in number of days of admission in this population. Additionally, the significance associated with this confidence interval is > 0.05 (p = 0.662), demonstrating no statistical significance.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-34). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in number of admissions per year becomes. Again, a negative net change denotes a higher number of admissions after clozapine has started.

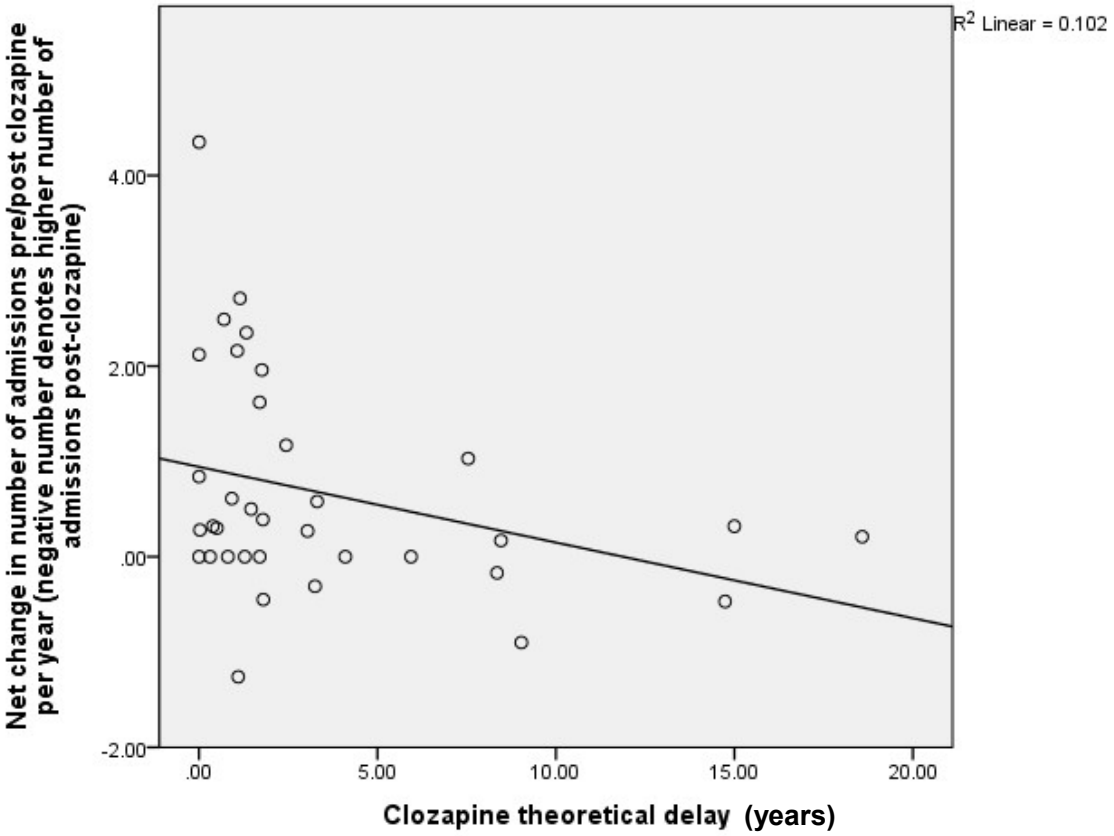

Figure 5-34 Scatterplot for change in number of admissions, clozapine discontinuers, method 4

The summary of the regression model is shown in Appendix G (Table 7-179). The table shows that the value of R is 0.320, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.102, meaning that the clozapine delay accounts for 10.2% of the variation in the change numbers of

admissions. Other variables must therefore account for the remaining 89.8% of the variation in the outcome variable.

Next, I conducted an analysis of variance (ANOVA). The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-180). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 3.765. This is non-significant at a *p* value of 0.061, and so the regression model does not predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-181). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.943, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.943. This means that a patient has 0.943 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as -0.079, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions will become more negative by 0.079 admissions per year of clozapine delay. Therefore 0.079 more admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 10.2% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for clozapine delay is non-significant at $p = 0.061$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the

theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-182). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.159 and -0.033. Since this interval does not include zero, there is a relationship between clozapine theoretical delay and net change in number of admissions in this population. However, the significance associated with this confidence interval is $p = 0.031$, demonstrating statistical significance.

5.3.5.3.5 Method 5

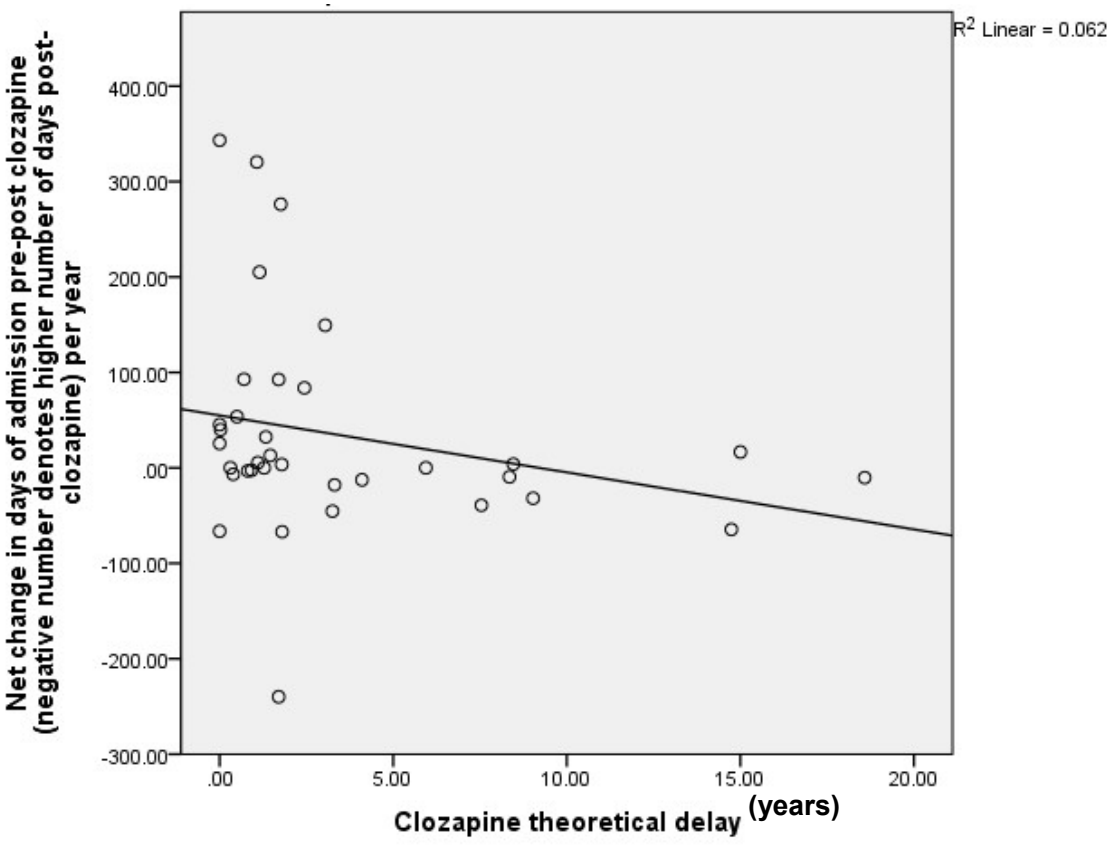

Figure 5-35 Scatterplot for change in days of admission, clozapine discontinuers, method 5

The scatterplot for the data is shown above (Figure 5-35). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net

change in days of admission per year becomes. Again, a negative net change denotes a higher number of days of admission after clozapine has started.

The summary of the regression model is shown in Appendix G (Table 7-183). The table shows that the value of *R* is 0.249, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in days of admission per year (the outcome variable) and clozapine delay. The R^2 is 0.062, meaning that the clozapine delay accounts for 6.2% of the variation in the change in days of admission. Other variables must therefore account for the remaining 93.8% of the variation in the outcome variable.

The results of the ANOVA are presented in Appendix G (Table 7-184). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is 2.176. This is non-significant at a *p* value of 0.150, and so the regression model does not predict net change in admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-185). The value of b_0 (the constant) is 54.970, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in admission days per year is 54.970. This means that 54.970 fewer days are spent as an inpatient in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as – 5.968, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in days of admission becomes more negative by 5.968 days. Therefore 5.968 more days of admission will be spent per year post-clozapine initiation. However, this model shows that clozapine delay accounts for 6.2% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are

shown in the final column of the table. The *t*-test for the predictor variable of clozapine delay is non-significant at $p > 0.05$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in days of admission per year.

The bootstrapped confidence intervals (Table 7-186) indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -11.913 and -2.213. Since this interval does not include zero, there is a genuine negative relationship between clozapine theoretical delay and net change in number of days of admission in this population. This result is significant at $p = 0.034$.

The linear regression is then repeated using the net change in the number of admissions per year as the dependent variable. The scatterplot for the data is shown below (Figure 5-36). A negative relationship is seen in the data, whereby the longer the delay in clozapine prescribing, the more negative the net change in number of admissions per year becomes. Again, a negative net change denotes a higher number of admissions after clozapine has started.

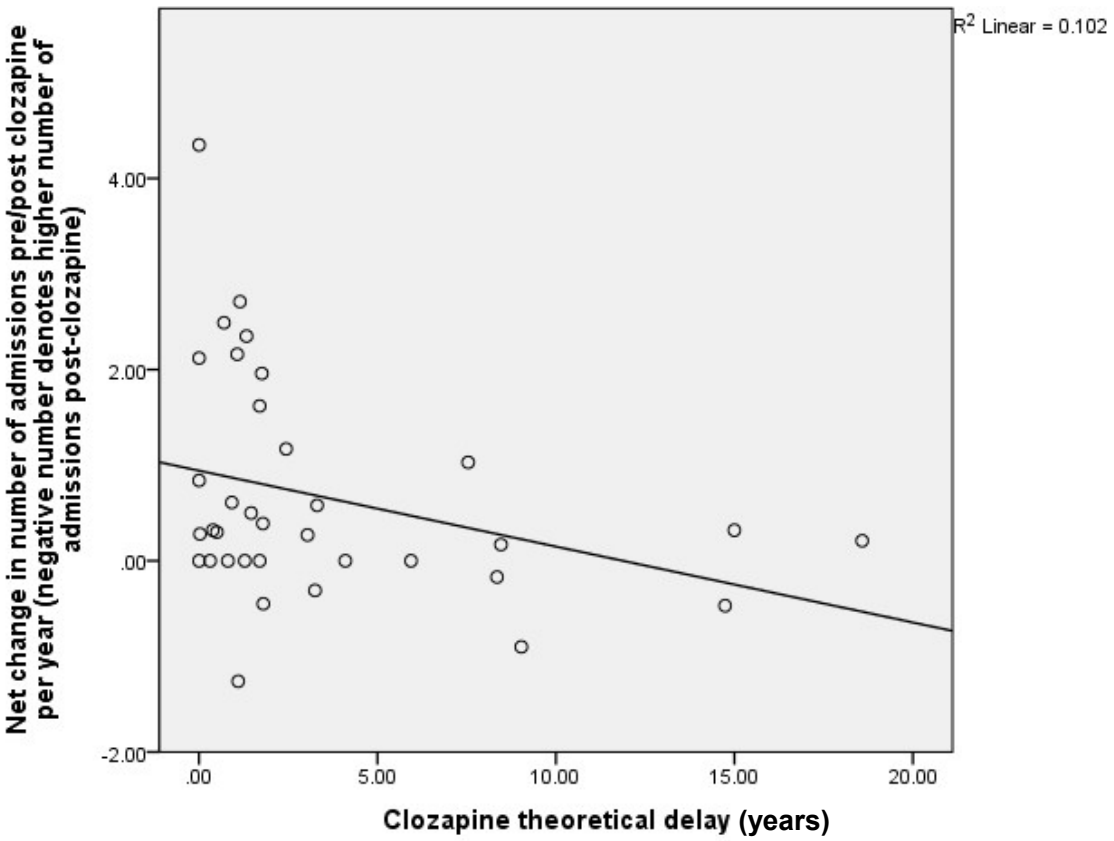

Figure 5-36 Scatterplot for change in number of admissions, clozapine discontinuers, method 5

The summary of the regression model is shown in Appendix G (Table 7-187). The table shows that the value of *R* is 0.320, and since there is only one predictor variable (clozapine delay), this value represents the simple correlation between the net change in number of admissions per year (the outcome variable) and clozapine delay. The R^2 is 0.102, meaning that the clozapine delay accounts for 10.2% of the variation in the change numbers of admissions. Other variables must therefore account for the remaining 89.8% of the variation in the outcome variable.

Next, I conducted an analysis of variance (ANOVA). The ANOVA investigates whether this model (with clozapine delay as a predictor variable) predicts the net change in admissions significantly better than simply using the mean net change in admissions would alone. The results are presented in Appendix G (Table 7-188). The sum of squares, associated degrees of freedom (df) and mean square are given in the table. From these data, the *F*-ratio is calculated, and shown as 3.765. This is non-significant at a *p* value of 0.061, and so the

regression model does not predict net change in numbers of admissions before and after starting clozapine significantly well.

The model parameters are presented in Appendix G (Table 7-189). These show the individual contribution of particular variables to the model (in this case, just the theoretical delay to clozapine prescribing). The value of b_0 (the constant) is 0.943, and so when the clozapine delay is zero (the x-axis intercept on the scatterplot), the model predicts that the net change in number of admissions per year is 0.943. This means that a patient has 0.943 fewer admissions in the year following clozapine initiation, compared to the year before clozapine was started. The gradient of the regression line (b_1) is given in the table as -0.079, and this shows the change in the outcome associated with a unit change in the predictor; therefore if clozapine delay is increased by 1 unit (1 year), the model predicts that the net change in admissions becomes more negative by 0.079 admissions per year, per extra year of clozapine delay. Therefore 0.079 more admissions will be spent per year post-clozapine initiation. However, this model shows that clozapine delay only accounts for 10.2% of the effect on the net change in admission days. The value of the regression co-efficient is also shown (*b*), and if this is significantly different to zero then this would confirm that the clozapine delay has a significant impact on the ability of the model to predict the net change in admissions per year. The significance of this is tested in the ANOVA using a *t*-test, the results of which are shown in the final column of the table. The *t*-test for clozapine delay is non-significant at $p = 0.061$, meaning that the regression coefficient (*b*) is not significantly different to zero, and the theoretical delay to clozapine use does not make a significant contribution to the outcome of the net change in admissions per year.

As discussed previously in this chapter and in chapter 2, the data may not conform to the parameters of a normal distribution, and so I also performed bootstrapping procedures to account for this. The results are shown in Appendix G (Table 7-190). The bootstrapped confidence intervals indicate that the population value for *b* (the regression coefficient) for clozapine theoretical delay is likely to lie between -0.160 and -0.038. Since this interval does not include zero, there is a relationship between clozapine theoretical delay and net change

in number of admissions in this population. However, the significance associated with this confidence interval is $p = 0.028$, demonstrating statistical significance.

Table 5-26 Clozapine discontinuers group, linear regression data summary

		Linear regression	ANOVA	Co-efficients		Bootstrapping	Effect of increasing delay to clozapine use by 1 year
		R^2	F	B_0	B_1		
Method 1	Change in days of admission	< 0.0005	0.001 (p = 0.977)	-32.775	0.097 (p = 0.977)	-4.642 to 5.594 (p = 0.970)	0.097 fewer days of admission per year after clozapine has started
	Change in number of admissions	0.102	3.765 (p = 0.061)	0.943	-0.079 (p = 0.061)	-0.170 to -0.031 (p = 0.027)*	0.079 more admissions per year after clozapine has started
Method 2	Change in days of admission	0.037	1.279 (p = 0.266)	11.724	-2.918 (p = 0.266)	-6.469 to -0.127 (p = 0.093)	2.918 more days of admission per year after clozapine has started
	Change in number of admissions	0.019	0.623 (p = 0.436)	0.359	0.015 (p = 0.436)	- 0.014 to 0.051 (p = 0.051)	0.015 fewer admissions per year after clozapine has started
Method 3	Change in days of admission	0.001	0.017 (p = 0.898)	-25.284	-0.435 (p = 0.898)	-5.171 and 4.694 (p = 0.842)	0.435 more days of admission per year after clozapine has started
	Change in number of admissions	0.102	3.765 (p = 0.061)	0.943	-0.079 (p = 0.061)	-0.170 to -0.028 (p = 0.026)*	0.079 more admissions per year after clozapine has started
Method 4	Change in days of admission	0.002	0.078 (p = 0.781)	-0.951	-0.951 (p = 0.781)	-6.453 to 4.577 (p = 0.662)	0.951 more days of admission per year after clozapine has started
	Change in number of admissions	0.102	3.765 (p = 0.061)	0.943	-0.079 (p = 0.061)	-0.159 to -0.033 (p = 0.031)*	0.079 more admissions per year after clozapine has started
Method 5	Change in days of admission	0.062	2.176 (p = 0.150)	54.970	-5.968 (p = 0.150)	-11.913 and -2.213 (p = 0.034)*	5.968 more days of admission per year after clozapine has started
	Change in number of admissions	0.102	3.765 (p = 0.061)	0.943	-0.079 (p = 0.061)	-0.160 to -0.038 (p = 0.028)*	0.079 more admissions per year after clozapine has started

*statistically significant at p >0.05

Table 5-26 summarises the data set out above. For all the methods of data analysis, clozapine delay predicts less than 11% of the net change in days of admission and number of admissions per year before and after clozapine initiation. None of the models reached statistical significance for the relationship between clozapine delay and net change in days of admission or net change in the number of admissions pre-and post-clozapine. Bootstrapped confidence intervals for methods 1, 3, 4 and 5 suggest a statistically significant relationship between clozapine delay and net change in number of admissions, and for method 5 also for the change in days of admission, but the models overall still lack statistical significance. If the delay to clozapine use is zero, there is a variation in the effect on the inpatient days and total admissions after clozapine has started depending on the data analysis method used. All methods predict a lower number of total admissions per year after clozapine has started, but some show an increase in the number of days of admission.

5.3.6 Multivariate analysis of variance

Mutivariate analysis of variance (MANOVA) allows testing of the difference between two groups (in this case, before and after clozapine), but with more than one outcome variable. This is therefore an extension of the above described linear regression, where only one outcome variable (the change in days or admission or number of admissions) was investigated. Further, the MANOVA can be used to investigate data with several independent variables. This is useful for this data set as investigations set out in chapter 2 suggested that some variables associated with the data (age, gender, diagnosis), in additional to the variable of theoretical clozapine delay already examined through ANOVA, may have an effect on the outcome variables.

Although I could conduct ANOVAs for each outcome variable (that is, for the net change in numbers of admissions as well as the change in days of admission presented above), this is not advisable as it risks type I errors occurring. Carrying out multiple statistical tests on the same data is not only bad practice, it also means that the effect of any relationship between the outcome variables is lost.

The dependent variables used for the MANOVA analysis (the outcome variables) were the net change in total admissions per year, and the net change in days of admission per year. It is sensible to include both these outcome variables in the same model, as they might be expected to affect each other, and the difference between them is clinically interesting. A large number of days of admission per year may reflect a few lengthy admission periods, or many short ones. Using only days of admission alone as an outcome variable cannot provide this level of information. The fixed factors for the MANOVA are grouping categories for the data that can be examined for effects on the outcome. These were chosen based on interesting results from the previous analyses (age, gender, ethnicity, diagnosis), or because they might logically be expected to affect the outcome variables (being a clozapine continuer or discontinuer; the number of previous antipsychotics taken). The fixed variable categories were grouped as follows in Table 5-27:

Table 5-27 MANOVA fixed variable categories

Fixed factor	**Categories**
Number of previous antipsychotics	1 to 2
	3 to 5
	6 to 10
	> 10
Age (years)	20 - 29
	30 - 39
	40 – 49
	50 – 59
	60 – 69
	70 – 79
Ethnicity	White
	Black
	Asian
	Mixed
	Other
Diagnosis	F20
	F25
	F31
	Other

I conducted the MANOVA first for the intent to treat group as a whole, then separately for clozapine continuers and discontinuers.

5.3.6.1 MANOVA – intent to treat group

5.3.6.1.1 Variables and factors

The number of patients in each category for the fixed factors is given in table in Appendix G (Table 7-191).

5.3.6.1.2 Testing assumptions

The MANOVA depends on four assumptions. Firstly, that the data are independent; that is, all residuals are statistically independent (residuals are the differences between the value a model predicts and the value actually seen in the data – in other words, the error associated with the model). Secondly, that the data were randomly sampled (in this case, the data set consists of the entire population. Characterisation of the excluded patients from the sample was completed in chapter 2). Thirdly, that the residuals have multivariate normality. Finally, that the variances in each group are roughly equal (homogeneity of covariance matrices), and that the correlation between the two outcome variables is the same in all groups.

The assumption of equality of covariance matrices can be tested using Box's test, which should be non-significant if the matrices are similar. The results from Box's test are less robust where the sample sizes within the population are different, and the table in Appendix G (Table 7-192) shows that this is the case. Unfortunately the only remedy for this is to delete random patients in the larger groups in order to achieve more similarly sized categories, but this causes a loss of power to the results. The results table shows Box's test to be non-significant at $p = 0.370$, therefore the covariance matrices can be assumed to be roughly equal.

5.3.6.1.3 MANOVA test statistics

The main MANOVA test statistics are presented in Appendix G (Table 7-193). The test results are given for the intercept of the model (where the MANOVA is characterised as a linear model) in the first row of the table, and then for each grouping variable in the subsequent rows. The statistics for the grouping variables give an indication of the influence of these variables on the outcome measures. There are four test statistics shown in the first

output column; Pillai's Trace, Wilk's Lambda, Hotelling's Trace, and Roy's Largest Root. Each differ in the robustness of their results. Roy's Largest Root is less reliable for platykurtic distributions (those with negative kurtosis) – previous analysis in this chapter showed the data to display positive kurtosis. Roy's Root is also not robust where the homogeneity of covariance matrices is untenable, in this case the Pillai's Trace statistic is more reliable. However, this statistic is affected by unequal sample sizes, as in this data set. This is why Box's test is important for this data analysis, and since this suggests that the covariance matrices can be assumed to be equal it is reasonable to assume that Pilliai's Trace is accurate.

In the second output column, the test statistics are converted into *F*-ratios (an indication of the overall difference between group means) with the corresponding degrees of freedom. The final column shows the significance values associated with the *F*-ratios for each test statistic. For gender, ethnicity, diagnosis, being a clozapine continuer or discontinuer and the number of antipsychotics used before clozapine, all the multivariate test statistics are non-significant at $p > 0.05$, suggesting that there are no between-group differences for the net change in admission days or admissions pre/post clozapine on these measures. For the variable of age, all the multivariate test statistics are significant, suggesting that there is a between-group difference for the net change in admission days or admissions pre/post clozapine for this variable. This result gives no information on the nature of this interaction, whether it affects both outcome variables or just one, and how the categories within the age group differ from each other. To investigate this further, univariate tests and discriminant function analyses are required.

5.3.6.1.4 Univariate test statistics

Levene's test of equality of variances has been described earlier in this thesis; briefly, it tests the assumption of homogeneity of variables for each of the outcome variables. The results are presented in Appendix G (Table 7-194), and are non-significant for the net change in the number of admissions pre/post clozapine per year ($p = 0.134$), but significant for the net change in days of admission pre/post clozapine per year ($p = 0.014$). This suggests that the

assumption of homogeneity of variance has not been met for this latter variable, and the multivariate test statistics may be less robust.

Next, an ANOVA summary table is shown in Appendix G (Table 7-195) for each of the dependent variables. An ANOVA is conducted for every fixed variable, and the corresponding residual sum of squares and total sums of squares. The *F*-ratio for each univariate ANOVA is given in the sixth column, and the significance value for this in the final column. The data show that age (p = 0.029) and being a clozapine continuer or discontinuer (p = 0.029) have a significant effect on the net change in days of admission pre-post clozapine per year. All other factors have no significant impact on either dependent variable.

5.3.6.1.5 MANOVA summary – intent to treat group

Using Pillai's trace, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, V = 0.73, F(10, 40) = 2.28, p = 0.032. Using Wilk's lambda, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, Λ = 0.40, F(10, 38) = 2.22, p = 0.038. Using Hotelling's trace statistic, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, T = 1.20, F(10, 36) = 2.15, p = 0.045. Using Roy's largest root, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, Θ = 0.81, F(5, 20) = 3.22, p = 0.027.

However, separate univariate ANOVAs on the outcome variables revealed significant age effects on the net change in days of admission pre-post clozapine per year, F(5, 20) = 3.17, p = 0.029 but a non-significant effect of age on the net change in number of admissions pre-post clozapine per year, F(5,20) = 2.01, p = 0.120.

Using Pillai's trace, there was no significant effect of clozapine continuation/discontinuation on the net change in days and numbers of admissions pre/post clozapine per year, V = 0.22, F(2, 19) = 2.76, p = 0.089. Using Wilk's lambda, there was no significant effect of clozapine continuation/discontinuation on the net change in days and numbers of admissions pre/post

clozapine per year, Λ = 0.78, F(2, 19) = 2.75, p = 0.089. Using Hotelling's trace statistic, there was no significant effect of clozapine continuation/discontinuation on the net change in days and numbers of admissions pre/post clozapine per year, T = 0.29, F(2, 19) = 2.75, p = 0.089. Using Roy's largest root, there was no significant effect of clozapine continuation/discontinuation on the net change in days and numbers of admissions pre/post clozapine per year, Θ = 0.29, F(2, 19) = 2.75, p = 0.089.

However, separate univariate ANOVAs on the outcome variables revealed significant clozapine continuation/discontinuation effects on the net change in days of admission pre-post clozapine per year, F(1, 20) = 5.51, p = 0.029 but a non-significant effect of clozapine continuation/discontinuation on the net change in number of admissions pre-post clozapine per year, F(1,20) = 3.80, p = 0.066.

A significant effect for clozapine continuation/discontinuation is seen for the univariate test but not the multivariate statistics. Previous analysis has shown that being a clozapine continuer results in a net decrease in the number of days of admission post-clozapine, but for clozapine discontinuers there is no difference after the drug is started. As the multivariate analysis does not distinguish between the variables within the clozapine continuer/discontinuer group, but the univariate analysis does, this may explain the difference in test statistics. However, the univariate test cannot take account of any correlation between the outcome variables; in order to evaluate this discriminant function analysis is required.

5.3.6.1.6 Discriminant function analysis - age

The MANOVA examines a linear combination of variables, and so where the MANOVA test statistics suggest a significant relationship is present, discriminant function analysis allows the linear combination to be examined in more detail. The MANOVA found statistically significant differences within the age and clozapine continuer/discontinuer groups, and so I followed both these variables up with discriminant analyses, dealing first with the age variable.

The first output table is shown in Appendix G (Table 7-196), and provides the eigenvalues for each variate. The variates are the linear combinations of the outcome variables. They are used to discriminate groups of patients; in this case, which age group they belong to, and so are called the discriminant function variates. The eigenvalues are equivalent to the *F*-ratios calculated in ANOVA analysis. The eigenvalues are then converted into the percentage of the variance they account for (third column in the table). The final column shows the canonical correlation, which, when squared, gives an effect size (synonymous to the R^2 value, explained earlier in the context of linear regression). The eigenvalues table shows that the first variate explains 91.4% of the variance, with a canonical R^2 of 0.095, whereas the second explains only 8.6%, with a canonical R^2 of 0.98.

The second output table (Table 7-197) shows the significance tests for both variates ('1 through 2') and the significance for the second variate, once the first has been removed (second row). Wilk's Lambda is the product of the unexplained variance of each of the variates. Large eigenvalues (which correspond to large experimental effects) produce small values for Wilks' Lambda, and so statistical significance is achieved when Wilks' Lambda is small. This table shows that neither the combination of variates or the second variate alone significantly discriminate the groups, as the significance values for both are > 0.05.

The next output table (Table 7-198) shows the canonical variate correlation coefficients, which indicate the relative contribution of each outcome variable to the discriminant function variates. For both variates, there is a positive relationship with the change in days of admission and number of admissions (all outcome values are positive). This means that both variates affect the changes in days and numbers of admissions in the same way. The output values can vary between -1 and 1, and so the results suggest that the change in days of admission has a slightly higher influence on the first variate, and the number of admissions has a larger influence on the second variate.

Finally, a combined-groups plot is presented in Appendix G (Figure 7-44). This plots the variate scores for each patient, grouped according to the age group to which the patient belonged. The group centroids are shown as blue squares; these are the mean variate

scores for each group. The discriminant function plot shows that the first function (across the horizontal axis) discriminates the extremes of age groups (20 – 29 and 60 – 79) from the 30 – 59 year old groups, and the second function (across the vertical axis) differentiates the older age groups (60 – 79) from the younger groups (20 – 59).

5.3.6.1.7 Summary – MANOVA for age

The MANOVA was followed up with discriminant analysis, which revealed two discriminant functions. The first explained 91.4% of the variance, canonical $R^2 = 0.095$, whereas the second explained only 8.6%, canonical $R^2 = 0.98$. In combination these discriminant functions did not significantly differentiate the groups, $\Lambda = 0.90$, $\chi^2(10) = 10.67$, $p = 0.384$, and removing the first function did not alter this result, $\Lambda = 0.99$, $\chi^2(4) = 0.954$, $p = 0.917$. The correlations between outcomes and the discriminant functions revealed that the net change in days of admission pre/post clozapine per year was not loaded evenly onto the two functions (r = 0.996 for the first function, and 0.090 for the second), but that the net change in days was loaded more highly onto the first function. The net change in number of admissions pre/post clozapine per year loaded more highly onto the second function (r = 0.853) than the first function (r = 0.552). The discriminant function plot shows that the first function discriminates the extremes of age groups (20 – 29 and 60 – 79) from the 30 – 59 year old groups, and the second function differentiates the older age groups (60 – 79) from the younger groups (20 – 59).

The MANOVA indicates that age can have a significant effect on the length of time spent in hospital after clozapine has been started. The ANOVA suggests that this effect is on the number of days of admission per year, but not on the total number of admissions per year. The discriminant analysis suggests that the separation within the age groups can best be explained in terms of one underlying dimension, and in this context the dimension is likely to be age itself, but finds this effect to be non-significant.

A histogram plotting the age categories against the mean net change in days of admission and number of admissions presented in Appendix G (Figure 7-45) shows that as age

increases from 20 – 49, the net change in the number of days of admission per year decreases. This means that the older patients are, the less benefit they obtain from clozapine initiation (the lower the net change in admission days after clozapine is initiated, the higher the number of days of admission). Of note, the bars for age groups 60 – 69 and 70 – 79 describe only one patient each, and therefore could be considered outliers. The net change in the number of admissions per year is minimal, and as found in the MANOVA not statistically significant.

This analysis found two apparently outlying results in the age categories 60 – 69 and 70 – 79, each of which contain only one patient each. There are two ways of dealing with these outlying results; firstly, to repeat the analysis removing these upper age categories and creating one >50 years category in replacement; and secondly to remove the outliers entirely from the analysis.

5.3.6.2 MANOVA, upper age categories combined

Here I have repeated the MANOVA analysis presented above but with one larger upper age category (> 50 years) to incorporate the outlying results found previously. The fixed variable categories for age are now:

- 20 – 29 years
- 30 -39 years
- 40 – 49 years
- > 50 years

The number of patients in each category for the fixed factors is given in table in Appendix G (Table 7-199).

5.3.6.2.1 Testing assumptions

The results from Box's test are shown in Appendix G (Table 7-200). The table shows Box's test to be non-significant at $p = 0.370$, therefore the covariance matrices can be assumed to be roughly equal.

5.3.6.2.2 MANOVA test statistics

The main MANOVA test statistics are presented in Appendix G (Table 7-201). For gender, ethnicity, diagnosis, being a clozapine continuer or discontinuer and the number of antipsychotics used before clozapine, all the multivariate test statistics are non-significant at $p > 0.05$, suggesting that there are no between-group differences for the net change in admission days or admissions pre/post clozapine on these measures. For the variable of age, all the multivariate test statistics are significant, suggesting that there is a between-group difference for the net change in admission days or admissions pre/post clozapine for this variable. This result gives no information on the nature of this interaction, whether it affects both outcome variables or just one, and how the categories within the age group differ from each other. To investigate this further, univariate tests and discriminant function analyses are required.

5.3.6.2.3 Univariate test statistics

Levene's test of equality of variances has been described earlier in this thesis; briefly, it tests the assumption of homogeneity of variables for each of the outcome variables. The results are presented in Appendix G (Table 7-202), and are non-significant for the net change in the number of admissions pre/post clozapine per year ($p = 0.139$), but significant for the net change in days of admission pre/post clozapine per year ($p = 0.014$). This suggests that the assumption of homogeneity of variance has not been met for this latter variable, and the multivariate test statistics may be less robust.

Next, an ANOVA summary table is shown in Appendix G (Table 7-203) for each of the dependent variables. The data show that age ($p = 0.009$) and being a clozapine continuer or discontinuer ($p = 0.029$) have a significant effect on the net change in days of admission pre-post clozapine per year. All other factors have no significant impact on either dependent variable.

5.3.6.2.4 MANOVA summary, upper age categories combined

Using Pillai's trace, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, V = 0.55, F(6, 40) = 2.54, *p* = 0.035. Using Wilk's lambda, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, Λ = 0.50, F(6, 38) = 2.62, *p* = 0.032. Using Hotelling's trace statistic, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, T = 0.89, F(6, 36) = 2.68, *p* = 0.030. Using Roy's largest root, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, Θ = 0.75, F(3, 20) = 5.01, *p* = 0.009.

However, separate univariate ANOVAs on the outcome variables revealed significant age effects on the net change in days of admission pre-post clozapine per year, F(3, 20) = 5.01, *p* = 0.009 but a non-significant effect of age on the net change in number of admissions pre-post clozapine per year, F(3,20) = 2.64, *p* = 0.077.

Using Pillai's trace, there was no significant effect of clozapine continuation/discontinuation on the net change in days and numbers of admissions pre/post clozapine per year, V = 0.22, F(2, 19) = 2.76, *p* = 0.089. Using Wilk's lambda, there was no significant effect of clozapine continuation/discontinuation on the net change in days and numbers of admissions pre/post clozapine per year, Λ = 0.78, F(2, 19) = 2.75, *p* = 0.089. Using Hotelling's trace statistic, there was no significant effect of clozapine continuation/discontinuation on the net change in days and numbers of admissions pre/post clozapine per year, T = 0.29, F(2, 19) = 2.75, *p* = 0.089. Using Roy's largest root, there was no significant effect of clozapine continuation/discontinuation on the net change in days and numbers of admissions pre/post clozapine per year, Θ = 0.29, F(2, 19) = 2.75, *p* = 0.089.

However, separate univariate ANOVAs on the outcome variables revealed significant clozapine continuation/discontinuation effects on the net change in days of admission pre-post clozapine per year, F(1, 20) = 5.51, p = 0.029 but a non-significant effect of clozapine

continuation/discontinuation on the net change in number of admissions pre-post clozapine per year, $F(1,20) = 3.80$, $p = 0.066$.

A significant effect for clozapine continuation/discontinuation is seen for the univariate test but not the multivariate statistics. Previous analysis has shown that being a clozapine continuer results in a net decrease in the number of days of admission post-clozapine, but for clozapine discontinuers there is no difference before or after the drug is started. As the multivariate analysis does not distinguish between the variables within the clozapine continuer/discontinuer group, but the univariate analysis does, this may explain the difference in test statistics. However, the univariate test cannot take account of any correlation between the outcome variables; in order to evaluate this discriminant function analysis is required.

5.3.6.2.5 Discriminant function analysis (age), upper age categories combined

The first output table is shown in Appendix G (Table 7-204), and provides the eigenvalues for each variate. The eigenvalues table shows that the first variate explains 99.6% of the variance, with a canonical R^2 of 0.044, whereas the second explains only 0.4%, with a canonical R^2 of 0.0002.

The second output table (Wilk's Lambda, Table 7-205) shows the significance tests for both variates ('1 through 2') and the significance for the second variate, once the first has been removed (second row). This table shows that neither the combination of variates or the second variate alone significantly discriminate the groups, as the significance values for both are > 0.05.

The next output table shows the canonical variate correlation coefficients (Table 7-206). For both variates, there is a positive relationship with the change in days of admission and number of admissions (all outcome values are positive). The results suggest that the change in days of admission has a slightly higher influence on the first variate, and the number of admissions has a larger influence on the second variate.

Finally, a combined-groups plot is presented in Appendix G (Figure 7-46 MANOVA, combined group plot, age variable combined, intent to treat group). The discriminant function plot shows little separation between the age groups across either outcome variable.

5.3.6.2.6 MANOVA - summary for age, upper age categories combined

The MANOVA was followed up with discriminant analysis, which revealed two discriminant functions. The first explained 99.6% of the variance, canonical $R^2 = 0.044$, whereas the second explained only 0.4%, canonical $R^2 = 0.0002$. In combination these discriminant functions did not significantly differentiate the groups, $\Lambda = 0.956$, $\chi^2(6) = 4.45$, $p = 0.617$, and removing the first function did not alter this result, $\Lambda = 1.00$, $\chi^2(2) = 0.017$, $p = 0.992$. The correlations between outcomes and the discriminant functions revealed that the net change in days of admission pre/post clozapine per year was not loaded evenly onto the two functions (r = 0.969 for the first function, and 0.246 for the second), but that the net change in days was loaded more highly onto the first function. The net change in number of admissions pre/post clozapine per year loaded more highly onto the second function (r = 0.919) than the first function (r = 0.313). The discriminant function plot shows little separation between the age groups.

The MANOVA indicates that age can have a significant effect on the length of time spent in hospital after clozapine has been started. The ANOVA suggests that this effect is on the number of days of admission per year, but not on the total number of admissions per year. The discriminant analysis suggests that the separation within the age groups can best be explained in terms of one underlying dimension, and in this context the dimension is likely to be age itself, but this result did not reach statistical significance.

A histogram plotting the age categories against the mean net change in days of admission and number of admissions presented in Appendix G (Figure 7-47 MANOVA histogram, age variable combined, intent to treat group) shows that as age increases from 20 – 49, the net change in the number of days of admission per year decreases. This means that the older patients are, the less benefit they obtain from clozapine initiation (the lower the net change

in admission days after clozapine is initiated). The new > 50 years category shows an increase again in the net change in admissions that is not in keeping with the general trend for the rest of the data. Observations from the scatterplot and inspection of the data suggest that this may be due to undue influence from the two outlying patients discussed previously in the upper age groups (60 – 69 and 70 – 79 years). The net change in the number of admissions per year is minimal, and as found in the MANOVA not statistically significant.

5.3.6.3 MANOVA – age outliers removed

This analysis removes the two outlying patients in the age category > 59 years in order to gauge the effect of these two patients on the overall result.

5.3.6.3.1 Fixed factors

The number of patients in each category for the fixed factors is given in table in Appendix G (Table 7-207).

5.3.6.3.2 Testing assumptions

The results from Box's test are shown in Appendix G (Table 7-208). The table shows Box's test to be non-significant at $p = 0.370$, therefore the covariance matrices can be assumed to be roughly equal.

5.3.6.3.3 MANOVA test statistics

The main MANOVA test statistics are presented in Appendix G (Table 7-209). For gender, ethnicity, diagnosis, being a clozapine continuer or discontinuer and the number of antipsychotics used before clozapine, all the multivariate test statistics are non-significant at $p > 0.05$, suggesting that there are no between-group differences for the net change in admission days or admissions pre/post clozapine on these measures. For the variable of age, all the multivariate test statistics are significant, suggesting that there is a between-group difference for the net change in admission days or admissions pre/post clozapine for this variable. This result gives no information on the nature of this interaction, whether it affects both outcome variables or just one, and how the categories within the age group differ

from each other. To investigate this further, univariate tests and discriminant function analyses are required.

5.3.6.3.4 Univariate test statistics

Levene's test of equality of variances has been described earlier in this thesis; briefly, it tests the assumption of homogeneity of variables for each of the outcome variables. The results are presented in Appendix G (Table 7-210), and are non-significant for the net change in the number of admissions pre/post clozapine per year (p = 0.128), but significant for the net change in days of admission pre/post clozapine per year (p = 0.012). This suggests that the assumption of homogeneity of variance has not been met for this latter variable, and the multivariate test statistics may be less robust.

Next, an ANOVA summary table is shown in Appendix G (Table 7-211) for each of the dependent variables. The data show that age (p = 0.016) and being a clozapine continuer or discontinuer (p = 0.029) have a significant effect on the net change in days of admission pre-post clozapine per year. For this analysis, age also has a significant effect on the net change in the number of admissions per year (p = 0.43). All other factors have no significant impact on either dependent variable.

5.3.6.3.5 MANOVA summary, age outliers removed

Using Pillai's trace, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, V = 0.60, F(6, 40) = 2.87, p = 0.020. Using Wilk's lambda, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, Λ = 0.48, F(6, 38) = 2.81, p = 0.023. Using Hotelling's trace statistic, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, T = 0.915, F(6, 36) = 2.75, p = 0.027. Using Roy's largest root, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, Θ = 0.66, F(3, 20) = 4.39, p = 0.016.

Separate univariate ANOVAs on the outcome variables revealed significant age effects on both the net change in days of admission pre-post clozapine per year, $F(3, 20) = 4.34$, $p = 0.016$, and the net change in number of admissions pre-post clozapine per year, $F(3,20) = 3.25$, $p = 0.043$.

Using Pillai's trace, there was no significant effect of clozapine continuation/discontinuation on the net change in days and numbers of admissions pre/post clozapine per year, $V = 0.22$, $F(2, 19) = 2.76$, $p = 0.089$. Using Wilk's lambda, there was no significant effect of clozapine continuation/discontinuation on the net change in days and numbers of admissions pre/post clozapine per year, $\Lambda = 0.78$, $F(2, 19) = 2.75$, $p = 0.089$. Using Hotelling's trace statistic, there was no significant effect of clozapine continuation/discontinuation on the net change in days and numbers of admissions pre/post clozapine per year, $T = 0.29$, $F(2, 19) = 2.75$, $p = 0.089$. Using Roy's largest root, there was no significant effect of clozapine continuation/discontinuation on the net change in days and numbers of admissions pre/post clozapine per year, $\Theta = 0.29$, $F(2, 19) = 2.75$, $p = 0.089$.

However, separate univariate ANOVAs on the outcome variables revealed significant clozapine continuation/discontinuation effects on the net change in days of admission pre-post clozapine per year, $F(1, 20) = 5.51$, $p = 0.029$ but a non-significant effect of clozapine continuation/discontinuation on the net change in number of admissions pre-post clozapine per year, $F(1,20) = 3.80$, $p = 0.066$.

A significant effect for clozapine continuation/discontinuation is seen for the univariate test but not the multivariate statistics. Previous analysis has shown that being a clozapine continuer results in a net decrease in the number of days of admission post-clozapine, but for clozapine discontinuers there is no difference before or after the drug is started. As the multivariate analysis does not distinguish between the variables within the clozapine continuer/discontinuer group, but the univariate analysis does, this may explain the difference in test statistics. However, the univariate test cannot take account of any correlation between the outcome variables; in order to evaluate this discriminant function analysis is required. Removing the two outlying age categories (>59 years) from the analysis now means that the

net change in number of admissions per year is also significantly different for the age categories, as well as net change in days of admission per year.

5.3.6.3.6 Discriminant function analysis (age), age outliers removed

The first output table is shown in Appendix G (Table 7-212), and provides the eigenvalues for each variate. The eigenvalues table shows that the first variate explains 99.2% of the variance, with a canonical R^2 of 0.051, whereas the second explains only 0.8%, with a canonical R^2 of 0.0004.

The second output table (Wilk's Lambda, Table 7-213) shows the significance tests for both variates ('1 through 2') and the significance for the second variate, once the first has been removed (second row). This table shows that neither the combination of variates or the second variate alone significantly discriminate the groups, as the significance values for both are > 0.05.

The next output table (Table 7-214) shows the canonical variate correlation coefficients. For both variates, there is a positive relationship with the change in days of admission and number of admissions (all outcome values are positive). The results suggest that the change in days of admission has a slightly higher influence on the first variate, and the number of admissions has a larger influence on the second variate.

Finally, a combined-groups plot is presented in Appendix G (Figure 7-48). The discriminant function plot shows little separation between the age groups across either outcome variable.

5.3.6.3.7 MANOVA summary for age, age outliers removed

The MANOVA was followed up with discriminant analysis, which revealed two discriminant functions. The first explained 99.2% of the variance, canonical $R^2 = 0.051$, whereas the second explained only 0.8%, canonical $R^2 = 0.0004$. In combination these discriminant functions did not significantly differentiate the groups, $\Lambda = 0.947$, $\chi^2(6) = 5.23$, $p = 0.510$, and removing the first function did not alter this result, $\Lambda = 1.00$, $\chi^2(2) = 0.042$, $p = 0.979$. The correlations between outcomes and the discriminant functions revealed that the net change

in days of admission pre/post clozapine per year was not loaded evenly onto the two functions (r = 0.020 for the first function, and -0.009 for the second), but that the net change in days was loaded more highly onto the first function. The net change in number of admissions pre/post clozapine per year loaded more highly onto the second function (r = 1.868) than the first function (r = -0.386). The discriminant function plot shows little separation between the age groups.

The MANOVA indicates that age can have a significant effect on the length of time spent in hospital after clozapine has been started. The ANOVA suggests that this effect is on both the number of days of admission per year and on the total number of admissions per year. The discriminant analysis suggests that the separation within the age groups can best be explained in terms of one underlying dimension, and in this context the dimension is likely to be age itself. This result remains statistically non-significant.

A histogram plotting the age categories against the mean net change in days of admission and number of admissions presented in Appendix G (Figure 7-49 MANOVA histogram, age outliers removed, intent to treat group) shows that as age increases from 20 – 49, the net change in the number of days of admission per year decreases. This means that the older patients are, the less benefit they obtain from clozapine initiation (the lower the net change in admission days after clozapine is initiated). The new > 50 years category shows a small decrease in the net change in admissions.

5.3.6.4 MANOVA - clozapine continuers

Next, I repeated the MANOVA presented above for clozapine continuers only.

5.3.6.4.1 Fixed factors

The number of patients in each category for the fixed factors is given in table in Appendix G (Table 7-215).

5.3.6.4.2 Testing assumptions

The results from Box's test are shown in Appendix G (Table 7-216). The table shows Box's test to be non-significant at $p = 0.692$, therefore the covariance matrices can be assumed to be roughly equal.

5.3.6.4.3 MANOVA test statistics

The main MANOVA test statistics are presented in Appendix G (Table 7-217). For gender, ethnicity, diagnosis, being a clozapine continuer or discontinuer and the number of antipsychotics used before clozapine, all the multivariate test statistics are non-significant at $p > 0.05$, suggesting that there are no between-group differences for the net change in admission days or admissions pre/post clozapine on these measures. For the variable of age, test statistics for Pillai's Trace, Wilk's Lambda and Hotelling's Trace for age are also non-significant, although Roy's largest root does reach significance. This result gives no information on the nature of this interaction, whether it affects both outcome variables or just one, and how the categories within the age group differ from each other. To investigate this further, univariate tests and discriminant function analyses are required.

5.3.6.4.4 Univariate test statistics

Levene's test of equality of variances has been described earlier in this thesis; briefly, it tests the assumption of homogeneity of variables for each of the outcome variables. The results are presented in Appendix G (Table 7-218), and are non-significant for the net change in the number of admissions pre/post clozapine per year ($p = 0.175$), but significant for the net change in days of admission pre/post clozapine per year ($p < 0.0005$). This suggests that the assumption of homogeneity of variance has not been met for this latter variable, and the multivariate test statistics may be less robust.

Next, an ANOVA summary table is shown in Appendix G (Table 7-219) for each of the dependent variables. The data show that none of the factors have a significant impact on either dependent variable.

5.3.6.4.5 MANOVA summary

Using Pillai's trace, there was no significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, V = 0.689, F(6, 26) = 2.276, *p* = 0.067. Using Wilk's lambda, there was no significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, Λ = 0.414, F(6, 24) = 2.216, *p* = 0.077. Using Hotelling's trace statistic, there was no significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, T = 1.166 F(6, 22) = 2.138, *p* = 0.089. However, using Roy's largest root, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, Θ = 0.886, F(3, 13) = 3.838, *p* = 0.036.

Separate univariate ANOVAs on the outcome variables revealed no significant age effects on either the net change in days of admission pre-post clozapine per year, F(3, 13) = 3.289, *p* = 0.055, or the net change in number of admissions pre-post clozapine per year, F(3, 13) = 3.106, *p* = 0.064.

5.3.6.4.6 Discriminant function analysis (age)

The first output table is shown in Appendix G (Table 7-220), and provides the eigenvalues for each variate. The eigenvalues table shows that the first variate explains 92.2% of the variance, with a canonical R^2 of 0.056, whereas the second explains only 7.8%, with a canonical R^2 of 0.0049.

The second output table (Wilk's Lambda, Table 7-221) shows the significance tests for both variates ('1 through 2') and the significance for the second variate, once the first has been removed (second row). This table shows that neither the combination of variates or the second variate alone significantly discriminate the groups, as the significance values for both are > 0.05.

The next output table (Table 7-222) shows the canonical variate correlation coefficients. For both variates, there is a positive relationship with the change in days of admission and number of admissions (all outcome values are positive). The results suggest that the change

in days of admission has a slightly higher influence on the first variate, and the number of admissions has a larger influence on the second variate.

Finally, a combined-groups plot is presented in Appendix G (Figure 7-50). The discriminant function plot shows little separation between the age groups across either outcome variable, with only a little separation for the youngest age group along the first function.

5.3.6.4.7 MANOVA, summary for age

The MANOVA was followed up with discriminant analysis, which revealed two discriminant functions. The first explained 92.2% of the variance, canonical $R^2 = 0.056$, whereas the second explained only 7.8%, canonical $R^2 = 0.0049$. In combination these discriminant functions did not significantly differentiate the groups, $\Lambda = 0.939$, $\chi^2(6) = 3.817$, $p = 0.701$, and removing the first function did not alter this result, $\Lambda = 0.995$, $\chi^2(2) = 0.304$, $p = 0.859$. The correlations between outcomes and the discriminant functions revealed that the net change in days of admission pre/post clozapine per year was not loaded evenly onto the two functions (r = 0.968 for the first function, and 0.249 for the second), but that the net change in days was loaded more highly onto the first function. The net change in number of admissions pre/post clozapine per year loaded more highly onto the second function (r = 0.928) than the first function (r = 0.372). The discriminant function plot shows separation between the 20 – 29 age group and the other age groups.

A histogram plotting the age categories against the mean net change in days of admission and number of admissions presented in Appendix G (Figure 7-51) shows that as age increases from 20 – 49, the net change in the number of days of admission per year decreases. This means that the older patients are, the less benefit they obtain from clozapine initiation (the lower the net change in admission days after clozapine is initiated). The 50 - 59 years category shows an increase again in the net change in admissions that is not in keeping with the general trend for the rest of the data.

The MANOVA indicates that for clozapine continuers, age can have a significant effect on the length of time spent in hospital after clozapine has been started. However, this result is

not seen in univariate analysis. The discriminant analysis suggests that the separation within the age groups can best be explained in terms of one underlying dimension, and in this context the dimension is likely to be age itself, although this did not reach statistical significance.

5.3.6.5 MANOVA – clozapine discontinuers

Next, I repeated the MANOVA presented above for clozapine discontinuers only.

5.3.6.5.1 Fixed factors

The number of patients in each category for the fixed factors is given in table in Appendix G (Table 7-223).

5.3.6.5.2 Testing assumptions

The results from Box's test are shown in Appendix G (Table 7-224). The table shows Box's test to be non-significant at $p = 0.212$, therefore the covariance matrices can be assumed to be roughly equal.

5.3.6.5.3 MANOVA test statistics

The main MANOVA test statistics are presented in Appendix G (Table 7-225). For ethnicity, age, and the number of antipsychotics used before clozapine, all the multivariate test statistics are non-significant at $p > 0.05$, suggesting that there are no between-group differences for the net change in admission days or admissions pre/post clozapine on these measures. For the variable of gender, all tests reach significance. For diagnosis, Roy's Largest Root gives a significant result. This result gives no information on the nature of this interaction, whether it affects both outcome variables or just one, and how the categories within the age group differ from each other. To investigate this further, univariate tests and discriminant function analyses are required.

5.3.6.5.4 Univariate test statistics

Levene's test of equality of variances has been described earlier in this thesis; briefly, it tests the assumption of homogeneity of variables for each of the outcome variables. The results are presented in Appendix G (Table 7-226), and are non-significant for the net change in the number of admissions pre/post clozapine per year (p = 0.186), and also non-significant for the net change in days of admission pre/post clozapine per year (p = 0.220). This suggests that the assumption of homogeneity of variance has been met for both variables.

Next, an ANOVA summary table is shown in Appendix G (Table 7-227) for each of the dependent variables. The data show that age, ethnicity, and the number of antipsychotics taken before clozapine have no significant impact on the net change in days of admission or number of admissions per year. However, gender and diagnosis both are found to have a statistically significant impact on both variables for gender, and on days of admission for diagnosis.

5.3.6.5.5 MANOVA summary

Using Pillai's trace, there was no significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, V = 0.203, F(4, 16) = 0.452, p = 0.770. Using Wilk's lambda, there was no significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, Λ = 0.797, F(4, 14) = 0.421, p = 0.791. Using Hotelling's trace statistic, there was no significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, T = 0.255, F(4, 12) = 0.382, p = 0.817. Using Roy's largest root, there was no significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, Θ = 0.255, F(2, 8) = 1.018, p = 0.404.

Using Pillai's trace, there was a significant effect of gender on the net change in days and numbers of admissions pre/post clozapine per year, V = 0.595, F(2, 7) = 5.145, p = 0.042. Using Wilk's lambda, there was a significant effect of gender on the net change in days and numbers of admissions pre/post clozapine per year, Λ = 0.797, F(2, 7) = 5.145, p = 0.042.

Using Hotelling's trace statistic, there was a significant effect of gender on the net change in days and numbers of admissions pre/post clozapine per year, T = 1.470, F(2, 7) = 5.145, *p* = 0.042. Using Roy's largest root, there was a significant effect of age on the net change in days and numbers of admissions pre/post clozapine per year, Θ = 0.1.470, F(2, 7) = 5.145, *p* = 0.042.

Using Pillai's trace, there was no significant effect of diagnosis on the net change in days and numbers of admissions pre/post clozapine per year, V = 0.617, F(4, 16) = 1.784, *p* = 0.181. Using Wilk's lambda, there was no significant effect of diagnosis on the net change in days and numbers of admissions pre/post clozapine per year, Λ = 0.410, F(4, 14) = 1.965, *p* = 0.155. Using Hotelling's trace statistic, there was no significant effect of diagnosis on the net change in days and numbers of admissions pre/post clozapine per year, T = 1.372, F(4, 12) = 2.058, *p* = 0.150. Using Roy's largest root, there was a significant effect of diagnosis on the net change in days and numbers of admissions pre/post clozapine per year, Θ = 1.322, F(2, 8) = 5.289, *p* = 0.034.

Separate univariate ANOVAs on the outcome variables revealed significant gender effects on both the net change in days of admission pre-post clozapine per year, F(2, 8) = 5.986, *p* = 0.040, and the net change in number of admissions pre-post clozapine per year, F(2, 8) = 11.760, *p* = 0.009. There were also significant diagnosis effects on the net change in days of admission pre-post clozapine per year, F (2, 8) = 5.255, *p* = 0.035, but not on the net change in number of admissions pre-post clozapine per year, F(2, 8) = 2.368, *p* = 0.156.

5.3.6.5.6 Discriminant analysis (age)

I followed the significant MANOVA findings for age, gender and diagnosis with discriminant analysis. The first, for age, is described below.

The first output table is shown in Appendix G (Table 7-228), and provides the eigenvalues for each variate. The eigenvalues table shows that the first variate explains 88% of the variance, with a canonical R^2 of 0.095, whereas the second explains only 12%, with a canonical R^2 of 0.014.

The second output table (Wilk's Lambda, Table 7-229) shows the significance tests for both variates ('1 through 2') and the significance for the second variate, once the first has been removed (second row). This table shows that neither the combination of variates or the second variate alone significantly discriminate the groups, as the significance values for both are > 0.05.

The next output table shows the canonical variate correlation coefficients (Table 7-230). For both variates, there is a positive relationship with the change in days of admission and number of admissions (all outcome values are positive). The results suggest that the change in days of admission has a slightly higher influence on the first variate, and the number of admissions has a larger influence on the second variate.

Finally, a combined-groups plot is presented in Appendix G (Figure 7-52). The discriminant function plot shows some separate between the age groups on function 1, and also some separation for the higher age group (50 – 59 years) along function 2. This is seen more clearly in the histogram presented in Appendix G (Figure 7-53), with the net change in days of admission becoming more negative with increasing age. A more negative net change corresponds to more days being spent in hospital after clozapine has started.

5.3.6.5.7 MANOVA summary for age

The MANOVA was followed up with discriminant analysis, which revealed two discriminant functions. The first explained 88.0% of the variance, canonical $R^2 = 0.095$, whereas the second explained only 12.0%, canonical $R^2 = 0.014$. In combination these discriminant functions did not significantly differentiate the groups, $\Lambda = 0.892$, $\chi^2(6) = 3.542$, $p = 0.738$, and removing the first function did not alter this result, $\Lambda = 0.986$, $\chi^2(2) = 0.442$, $p = 0.802$. The correlations between outcomes and the discriminant functions revealed that the net change in days of admission pre/post clozapine per year was not loaded evenly onto the two functions (r = 0.998 for the first function, and 0.065 for the second), but that the net change in days was loaded more highly onto the first function. The net change in number of admissions pre/post clozapine per year loaded more highly onto the second function (r =

0.847) than the first function (r = 0.531). The discriminant function plot shows separation between all age groups.

The MANOVA and univariate statistics indicate that for clozapine discontinuers, age has no significant effect on the length of time spent in hospital after clozapine has been started. The discriminant analysis shows wide scatter across the variables, again indicating no significant relationship, although the histogram (Figure 7-53) shows that the trend is for increasing age to mean more days spent in hospital after starting clozapine.

5.3.6.5.8 Discriminant analysis (gender)

The first output table is shown in Appendix G (Table 7-231), and provides the eigenvalues for the variate. The gender variable consists of only two categories, and so the eigenvalues table shows that the data were described by only one variate explaining 100% of the data, with a canonical R^2 of 0.040.

The second output table (Wilk's Lambda, Table 7-232) shows the significance tests for the variate, and shows that this variate did not significantly discriminate the groups, as the significance value is > 0.05.

The next output table shows the canonical variate correlation coefficients (Table 7-233). For the variates, there is a positive relationship with the change in days of admission and number of admissions (all outcome values are positive). The results suggest that the change in days of admission has a slightly higher influence.

Finally, a histogram presented in Appendix G (Figure 7-54) shows a positive net change in days of admission for male clozapine discontinuers, and a negative net change in days of admission for female clozapine discontinuers. However, this difference is not statistically significantly different as demonstrated in the previous tests.

5.3.6.5.9 MANOVA, summary for gender

The MANOVA was followed up with discriminant analysis, which revealed one discriminant function. This function explained 100% of the variance, canonical R^2 = 0.040. This

discriminant function did not significantly differentiate the groups, $\Lambda = 0.960$, $\chi^2(2) = 1.318$, $p = 0.517$. It is important to note that there were statistically significantly more men than women in the discontinuation group compared to continuers.

The MANOVA indicates that for clozapine discontinuers, gender has no significant effect on the length of time spent in hospital after clozapine has been started (and that the significant result seen in the univariate ANOVA is therefore likely to be a false positive). The histogram presented in Appendix G (Figure 7-54) suggests that female discontinuers are more likely to have a negative net change in days of admission after starting clozapine, but this result is not statistically significant.

5.3.6.5.10 Discriminant function analysis (diagnosis)

The first output table is shown in Appendix G (Table 7-234), and provides the eigenvalues for each variate. The eigenvalues table shows that the first variate explains 72.2% of the variance, with a canonical R^2 of 0.082, whereas the second explains only 27.8%, with a canonical R^2 of 0.033.

The second output table (Wilk's Lambda, Table 7-235) shows the significance tests for both variates ('1 through 2') and the significance for the second variate, once the first has been removed (second row). This table shows that neither the combination of variates nor the second variate alone significantly discriminate the groups, as the significance values for both are > 0.05.

The next output table shows the canonical variate correlation coefficients (Table 7-236). For both variates, there is a positive relationship with the change in days of admission and number of admissions (all outcome values are positive). The results suggest that the change in days of admission has a slightly higher influence on the first variate, and the number of admissions has a larger influence on the second variate.

Finally, a combined-groups plot is presented in Appendix G (Figure 7-55). The discriminant function plot shows separation between the diagnostic groups principally on function 1. This

is seen more clearly in the histogram presented in the Appendix G (Figure 7-56), with the net change in days of admission becoming more negative for those with a diagnosis of schizoaffective disorder. A more negative net change corresponds to more days being spent in hospital after clozapine has started.

5.3.6.5.11 MANOVA, summary for diagnosis

The MANOVA was followed up with discriminant analysis, which revealed two discriminant functions. The first explained 72.2% of the variance, canonical $R^2 = 0.082$, whereas the second explained 27.8%, canonical $R^2 = 0.033$. In combination these discriminant functions did not significantly differentiate the groups, $\Lambda = 0.887$, $\chi^2(4) = 3.783$, $p = 0.436$, and removing the first function did not alter this result, $\Lambda = 0.967$, $\chi^2(1) = 1.072$, $p = 0.301$. The correlations between outcomes and the discriminant functions revealed that the net change in days of admission pre/post clozapine per year was not loaded evenly onto the two functions (r = 0.999 for the first function, and 0.554 for the second), but that the net change in days was loaded more highly onto the first function. The net change in number of admissions pre/post clozapine per year loaded more highly onto the second function (r = 0.832) than the first function (r = 0.043). The discriminant function plot shows separation between all diagnostic groups, but the points are widely scattered.

The MANOVA indicates that for clozapine discontinuers, diagnosis has no significant effect on the length of time spent in hospital after clozapine has been started. The discriminant analysis suggests that there is separation within the diagnostic groups and that this can best be explained in terms of one underlying dimension, and in this context the dimension is likely to be diagnosis itself, but this result is not statistically significant. The univariate ANOVA analysis is therefore likely to be a false positive result.

5.4 Summary

Analysis of the intent to treat population found a statistically significant difference between the number of admissions per year before and after clozapine had started. All methods of

data analysis found a reduction in the mean number of admissions per year after clozapine initiation, with a range of a reduction of 0.34 to 0.73 admissions per year. A statistically significant difference between the number of days of admission per year pre-clozapine initiation compared to the number of days of admission per year post-clozapine initiation was also found when the portion of the index admission that remained after clozapine was started was either entirely discounted, or at least the first 14 days of this post-clozapine index admission was removed from analysis. This could be explained by a proportion of patients starting on clozapine, but then stopping before the end of the index admission, elongating this post-clozapine period and reducing the proportional difference between the pre- and post-clozapine admission days per year. If this were the case however, this difference would be expected to remain evident in subgroup analysis of clozapine discontinuers, but be eliminated for clozapine continuers – this is not the case. The net change in days of admission varied widely depending on the method of data analysis used, being most marked for methods 2 (a reduction of 16.74 days) and 5 (a reduction of 47.31 days), where the post-clozapine portion of the index admission was excluded from analysis.

There was a statistically significant difference between the number of admissions per year pre- and post-clozapine for clozapine continuers, regardless of how the data were analysed. In other words, if you keep taking the clozapine, you have fewer admissions per year than you did before you started the clozapine. The median reduction in the number of admissions per year was 0.77, representing an 78% reduction from the median number of admissions per year pre-clozapine (0.88). There was also a statistically significant difference in days of admission per year pre- and post-clozapine for clozapine continuers, with a median reduction of 23.19 days per year. The smallest net change was seen in data analysis method 1, where the entire post-clozapine section of the index admission was included in data analysis. This again suggests that this post-clozapine period is proportionally long – it may be that time to discharge is lengthy once clozapine is initiated, above the 2 week titration period (method 4, which attributed this fortnight to the pre-clozapine period, retained statistical difference between the pre- and post-data and found a larger net change in days of admission per year).

It is possible that there is a latency to clozapine response, which contributes to this time to discharge.

For clozapine discontinuers, there was no statistically significant difference between days of admission pre- and post-clozapine unless the entire post-clozapine index admission time is attributed to the post-clozapine period (method 1), where the number of days of admission per year post-clozapine is higher than that pre-clozapine. This is difficult to explain, but may be due to a heterogeneous sample of clozapine discontinuers; patients discontinued clozapine at different time points (some may have discontinued during the index admission) but were analysed as one group. It is also possible that patients that go on to discontinue clozapine are more likely to have fewer days of admission per year pre-clozapine than post-clozapine; this is reflected in the net change in days of admission being negative for 3 of the methods of analysis, but positive for all methods for clozapine continuers. This means that discontinuing clozapine means you are likely to have more days of admission after starting it. If you continue clozapine, this is reversed (you have more days of admission before the clozapine than after). If you stop taking the clozapine, then you spend more days as an inpatient after the date you originally started the clozapine compared to before you took it, unless you ignore the time period spent during the index admission once clozapine had been started. If you ignore this, then you spend more time as an inpatient per year before you started the clozapine compared to afterwards. This effect is lessened if you ignore the entire index admission (method 2) compared to ignoring only the post-clozapine index admission period (method 5). For all data analysis methods except method 2 (disregarding the entire index admission), a reduction of the number of admissions per year of 0.66 was shown after clozapine initiation. This represents a 62% reduction, lower than that seen for clozapine continuers.

Whether you stop or continue clozapine and regardless of the method used to analyse the data, the number of admissions per year is lower after clozapine has been started compared to before. However, continuing clozapine leads to fewer inpatient admissions after the clozapine has been started compared to stopping the clozapine. Continuing clozapine also

leads to a reduction in the number of days of admission per year, whereas if clozapine is discontinued, this effect is lost. For clozapine continuers therefore, not only might they experience fewer admissions per year, but those admissions may also be shorter.

From z-score calculation, less than 95% of the data fall within the normal distribution range for all analysis methods except 2 and 4. The reason for this bias is partly the presence of outliers within the sample population. These are cases where the entire study period falls within the index admission, resulting in the patient appearing to be an inpatient for the entirety of their history. There are further cases where either the entire pre-clozapine period or the entire post-clozapine period are spent as an inpatient, again giving the appearance of much higher proportions of inpatient stay per year than is perhaps really the case. This problem is usually encountered where the length of the study period is relatively short, caused by a relatively short time period between the start of the illness and clozapine initiation. This is likely to mean that patients who experience a shorter clozapine delay (the sooner clozapine is started in an illness course the less likely a lengthy clozapine delay, although this is not necessarily always the case – patients could receive 3 antipsychotics in quick succession and then wait a long time for clozapine. Generally though this tends not to be the prescribing pattern) may appear to have more inpatient stays per year than is truly representative. If clozapine delay is associated with inpatient stay, then this will lessen the apparent strength of this result. This type of outlier (where the entire study period lies entirely within the index admission) is removed from one end of the scale (100% admission) for method 2, as this method discounts the index admission from analysis. These cases will instead appear to have 0% admissions during their entire illness. It may be that the central limit theorem means that the population may be considered normally distributed, and Levene's test (although of less importance for large groups) broadly supports this. Nonetheless, I have reported non-parametric tests where the data are assessed to be non-normal.

In analysis of the effect of clozapine delay on the net change in days of admission pre- and post-clozapine initiation, regression models for the intent to treat population found the delay to account for less than 10% of the net change. This was true for clozapine continuers when

analysed as a subgroup, and also for discontinuers. Of the intent to treat group models that reached statistical significance, all predicted that an increase in the delay to clozapine use results in more days of admission or total admissions per year once clozapine had started. No models for the clozapine continuers subgroup reached statistical significance, although all methods of data analysis predicted a lower number of days of admission and total admissions per year after clozapine had started if the delay to starting was zero. It was also the case that no models for the clozapine discontinuers group reached statistical significance, but some variation was seen in the effect on the number of days of admission after clozapine initiation when the delay to clozapine was zero; some predicted an increase, some a decrease. All predicted a reduction in the total number of admissions per year.

Multivariate analysis of variance of the intent to treat group found no effect of the number of pre-clozapine antipsychotics, gender, ethnicity or diagnosis on the net change in admission (days or total episodes) in the pre-clozapine compared to the post-clozapine period. A significant effect of age was revealed, finding that increasing age conferred a reduction in the net change in number of days of admission per year. Older patients therefore saw a reduced benefit from clozapine. This observation held true for those who continued to take clozapine only – for those who discontinued clozapine there was no significant effect of age. It is possible that this is due to the smaller effect size in the population that discontinued, and the smaller patient numbers in this group – a larger study may find a significant effect as seen in the continuing group. Of note, the significant result found in the multivariate analysis was not significant in the following discriminant function analysis, which suggested that the net change in days of admission or admissions after clozapine initiation were not discriminated by age.

Those that discontinued clozapine were also significantly separated in diagnosis – patients with a diagnosis of schizoaffective disorder (F25) had a negative net change in days of admission, showing an increase in days of admission after clozapine initiation. There was also a significant effect of gender, with women that discontinued clozapine having an overall net negative change in days of admission after clozapine initiation, showing that more days

were spent in hospital after clozapine was started compared with before. The clozapine discontinuers group contained a significantly higher proportion of men, so this result is based on a small number of female clozapine discontinuers (n = 8). Again, these results were not significant in discriminant function analysis.

In conclusion, taking clozapine reduces both the number of days per year you spend as an inpatient, and also the number of admissions you have per year, compared to the time before you started clozapine. If you stay on the clozapine, this reduction in inpatient stay is greater than if you start it, but then stop. The amount of time it takes from the time a patient is eligible for clozapine, to the time it is actually prescribed, makes no difference to the reduction in admission days and total admissions a patient can expect once the clozapine has started. Younger patients derive more benefit from clozapine when measured in time spent as an inpatient.

5.5 Publications arising from this study

See Appendix I: **Siobhan Gee**, Sukhwinder Shergill and David Taylor (2016) Factors associated with changes in hospitalisation in patients prescribed clozapine. *Journal of Psychopharmacology*, 30(8):819-25

6 Factors influencing clozapine discontinuation

6.1 Introduction

Clozapine remains the antipsychotic of choice in treatment-resistant schizophrenia (20). Despite its superior efficacy in refractory illness compared with other antipsychotics (183), as described in chapter 2 it is used less frequently and later in treatment than recommended (148). There is no doubt that, in terms of managing the symptoms, the use of antipsychotic medication improves outcomes compared to placebo (184), and in the management of treatment-refractory schizophrenia, clozapine is superior to other antipsychotic medication (183). Poor control of symptoms is significantly harmful, not only to patients with respect to their quality of life (185), but also has a considerable financial impact on healthcare resource (186). One of the main difficulties is ensuring patient continuation with treatment. As shown in chapter 5, those who persist with clozapine treatment show a large reduction in hospital bed days (187).

The costs of clozapine therapy largely occur at the beginning of treatment. Baseline blood tests, weekly blood count monitoring, possible inpatient admissions or intensive home input for titration are all largely within the first 18 weeks of treatment. Should clozapine therapy be successful, over a period of time it is expected that this cost will be recouped as the length of time the patient remains in the community increases, with no inpatient admissions, a reduction in the intensity and frequency of healthcare professionals input, and increased contribution to society through improved social and occupational functioning. I have shown that discontinuing clozapine is likely to lead to increased illness severity. Clearly the savings to the NHS, as well as the clinical benefits to the patient, therefore only remain if the patient continues to comply with clozapine treatment.

I examined the reasons for clozapine discontinuation in a cohort of patients in South East London, with the aim of identifying factors that may predict the likelihood of stopping treatment. Previous studies have found that age (56, 102-104, 109) and ethnicity (77, 102,

103, 111, 118) may affect the likelihood of clozapine discontinuation. I have previously shown that there is a wide variation in delay to accessing clozapine and the number of antipsychotics used prior to clozapine within this population (148). I hypothesise that these factors, along with gender and diagnosis might also affect the risk of clozapine discontinuation.

6.1.1 Objectives

- To establish what proportion of patients discontinue clozapine.
- To describe clozapine discontinuation and restart patterns.
- To investigate the effect of a patient's age, ethnicity, diagnosis, length of theoretical delay to starting clozapine, and number of previous non-clozapine antipsychotics on the likelihood of discontinuing clozapine.

6.2 Method

All patients who commenced clozapine for the first time between 1st January 2006 and 15th April 2010 at SLaM were included in the study. Data extraction methods and definitions have been described in detail previously in chapter 2; in brief, ethnicity, duration of illness and treatment history were extracted from the clinical notes. Patients under the care of forensic services were included in the cohort for this study. Adequate antipsychotic treatment episodes were defined as the prescription of a regular daily dose of an antipsychotic at or above a minimum therapeutic dose for at least 6 weeks. The maximum theoretical delay in clozapine initiation was defined as the time from the end of the second adequate antipsychotic treatment episode to first clozapine use. Where clinical notes were missing, so precluding a complete prescribing history, patients were excluded from the analysis.

Patients were classified as 'discontinuers' where clozapine was stopped at least once during the time of the study. Clozapine discontinuation was established from the review of the clinical notes. Clozapine was classified as 'discontinued' where its cessation was followed by a deliberate switch to a different medication. Periods of non-compliance followed by re-

titration directly onto clozapine were not considered as clozapine 'discontinuation', even if another antipsychotic was used to 'cover' the re-titration period. Short term use of other antipsychotics pending re-titration to clozapine were also not considered as 'discontinuation', where it was clear from the clinical notes that the intention was to re-titrate, and the delay was caused only by practical or logistical reasons.

Patients were included in the 'discontinuation' group if they discontinued clozapine (as defined above) at any point during the study period. This included patients who discontinued clozapine and were never restarted, but also those with other patterns of discontinuation – those who stopped for a period of time but were later restarted, and those who repeated this discontinuation/restart pattern multiple times. The reason for the discontinuation, the antipsychotic(s) switched to, and cause of death where applicable, was taken from the clinical notes. Patients who did not stop clozapine at any time were classified as 'continuers'. Patients were counted as 'continuers' until they were censored (lost to follow up, LTFU) or the study ended (01.11.14).

6.2.1 Statistical analysis

Data were analysed using SPSS version 22. Clozapine continuers and discontinuers were compared using t-tests and chi-squared tests. Binary logistic regression was used to investigate variables that may predict clozapine discontinuation. Categorical predictor variables were gender, ethnicity and diagnosis. Continuous predictor variables were age, length of clozapine delay, and number of antipsychotics prescribed previous to clozapine initiation. Multiway crosstabulations were performed for all categorical variables, and ethnicity and diagnosis categories collapsed where necessary to avoid violating assumptions. Sequential models were analysed using each variable as a single predictor.

6.3 Results

Of the total sample of 133 patients, 48 discontinued clozapine during the study period. From the total sample, 31 patients were under the care of forensic services; of which 13

discontinued clozapine. Five patients from the original data set had died at the time of the second study end point. These patients were removed from the current analysis.

I performed a *t*-test for continuous variables (age, gender, clozapine delay, number of prescriptions prior to clozapine) and a chi-squared test for variables with more than 2 categories (ethnicity and diagnosis) to establish whether the two groups (clozapine continuers and discontinuers) differed in terms of these variables. The results of these tests are presented in Appendix H (Table 7-237, Table 7-238, Table 7-239) and the resulting *p* values shown in the final column of the table below (Table 6-1). As described previously in this thesis, where Levene's test is not significant (also presented in Appendix H, Table 7-237), the variances of the two groups are roughly equal and the assumption of homogeneity of variances is tenable. Levene's test is significant for gender, and so equal variances for this variable should not be assumed.

Table 6-1 Demographics

		Continuers (*n* = 85)	**Discontinuers (*n* = 48)**	***p***
Male, *n* (%)		53 (62.4)	40 (83.3)	0.007
Mean age, years		37.87 (range 20 – 78)	34.63 (range 17 – 59)	0.072
Diagnosis, *n* (%)	F20	58 (68.2)	33 (68.8)	0.335
	F25	13 (15.3)	7 (14.6)	
	F31	6 (7.1)	3 (6.3)	
	Other	8 (9.4)	5 (10.4)	
Clozapine theoretical delay, years		4.00 (range 0 – 18)	3.73 (range 0 – 19)	0.741
Total number of antipsychotic prescriptions before clozapine		5.60 (range 1 – 24)	5.44 (range 1 – 18)	0.813

The details of the clozapine discontinuation events are shown in Table 6-2 and Figure 6-1 below.

Table 6-2 Medication stop and switch details

		***N* (%)**
Total number of clozapine stops	1	34 (70.8)
	2	10 (20.8)
	3	4 (8.3)
	4	2 (4.2)
First drug switched to	Olanzapine	13 (27.1)
	Amisulpride	10 (20.8)
	Risperidone	10 (20.8)
	Aripiprazole	4 (8.3)
	Flupenthixol	3 (6.3)
	Haloperidol	2 (4.2)

		***N* (%)**
	Quetiapine	2 (4.2)
	Aripiprazole + olanzapine	1 (2.1)
	Zuclopenthixol	1 (2.1)
	Pipothiazine	1 (2.1)
	Nothing	1 (2.1)
First formulation switched to	Oral	39 (81.3)
	Depot	8 (16.7)
	Nothing	1 (2.1)
First drug class switched to	Typical	7 (14.6)
	Atypical	40 (83.3)
	Nothing	1 (2.1)
Reason for first stop	Patient refusing	29 (60.4)
	Red blood result	9 (18.8)
	Patient refusing due to side effects	4 (8.3)
	Patient refusing blood tests	3 (6.3)
	Medical requirement	2 (4.2)
	Diagnosis changed	1 (2.1)
Clozapine restarted after first stop	Yes	34 (70.8)
	No	14 (29.2)
Second drug switched to	Pipothiazine	2 (14.3)
	Olanzapine	2 (14.3)
	Risperidone	2 (14.3)
	Flupenthixol	2 (14.3)
	Haloperidol	2 (14.3)
	Zuclopenthixol	2 (14.3)
	Amisulpride	1 (7.1)
	Paliperidone	1 (7.1)
Second formulation switched to	Oral	6 (42.9)
	Depot	8 (57.1)
Second drug class switched to	Typical	8 (57.1)
	Atypical	6 (42.9)
Reason for second stop	Patient refusing	11 (78.6)
	Patient refusing due to side effects	2 (14.3)
	Red blood result	1 (7.1)
Clozapine restarted after second stop	Yes	10 (71.4)
	No	4 (28.6)
Third drug switched to	Risperidone	2 (50.0)
	Flupenthixol	1 (25.0)
	Quetiapine	1 (25.0)
Third formulation switched to	Oral	3 (75.0)
	Depot	1 (25.0)
Third drug class switched to	Typical	1 (25.0)
	Atypical	3 (75.0)
Reason for third stop	Patient refusing	3 (75.0)
	Red blood result	1 (25.0)
Clozapine restarted after third stop	Yes	2 (50.0)
	No	2 (50.0)
Fourth drug switched to	Olanzapine	1 (50.0)
	Risperidone	1 (50.0)
Fourth formulation switched to	Oral	2 (100.0)
Fourth drug class switched to	Atypical	2 (100.0)
Reason for fourth stop	Patient refusing	1 (50.0)
	Red blood result	1 (50.0)
Clozapine restarted after fourth stop	No	2 (100.0)
Total number of clozapine restarts	0	14 (29.2)

		***N* (%)**
	1	24 (50.0)
	2	8 (16.7)
	3	2 (4.2)

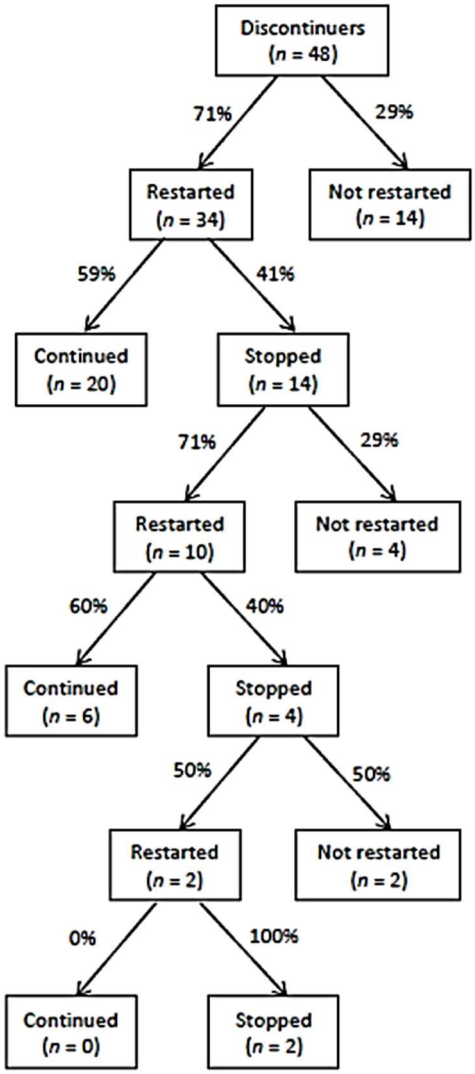

Figure 6-1 Medication stop and switch details

6.3.1 Binary logistic regression

Binary logistic regression is logistic regression where the outcome variable has two categories (in this case, being a clozapine continuer or discontinuer). In this context, logistic regression can be used to predict the outcome (discontinuing or continuing clozapine) from a combination of categorical and continuous predictor variables. The categorical predictor variables for this analysis are gender, ethnicity, and diagnosis. The continuous predictor variables are age, the length of the delay to starting clozapine, and the number of previous

antipsychotics given. The aim is to establish whether any of these variables in combination can predict the likelihood of a patient stopping clozapine.

It is first important to produce contingency tables for the categorical variables. This process has been described previously in this thesis. Briefly, the goodness-of-fit tests when performing logistic regression assume that each possible combination of categories contains an expected result of at least 1, and no more than 20% of the combinations contain expected frequencies of results of less than 5. This is checked by performing multiway crosstabulations of the data, and the results tables for these are presented in Appendix H.

The first crosstabulations table is for gender and ethnicity (Table 7-240), and it is evident that several expected counts are below 1, and many are below 5. The power of the test is therefore reduced. Remedies to this include; collecting more data (this is not possible), accepting this loss of power (this is not desirable), or merging some of the categories within the variables to create larger categories that would avoid having too few expected frequencies. The same situation can be seen in the second crosstabulations table (which examines gender and diagnosis, Table 7-241), where 27% of the expected count frequencies are below 5. In order to solve this problem and improve the strength of the subsequent statistical tests, I merged the ethnicity categories as chosen in previous chapters into:

- White
- Black
- Asian
- Mixed
- Other

The next crosstabulation table shown in Appendix H (Table 7-242) outlines the results from the new ethnicity categories. Unfortunately, some expected counts within the cells remain unacceptably low (below 1). A further merge of the categories was required, creating the following categories:

- White
- Black
- Other

The results from this second category merge are shown in the next crosstabulation table in Appendix H (Table 7-243), and produces 3 expected counts below 5 (8% of the total), and no counts below 1. This is an acceptable result and so these new categories for the ethnicity variable should be used for the subsequent analyses.

In order to address the problems with the diagnosis category, I merged the categories into:

- F20
- F25
- Other

The results of the crosstabulations for this can be seen in Appendix H (Table 7-244). This table shows 4 expected counts to be below 5, which is an acceptable 11% of the total. None are below 1.

As I had no clear, evidence-based or theoretical reason to logically expect any one variable to predict the likelihood of discontinuing clozapine over any of the other variables, I chose first to enter the predictor variables individually and sequentially into the logistic regression, in order to gauge the magnitude of effect each had on the outcome alone. The variables used in each model are shown below in Table 6-3:

Table 6-3 Sequential binary logistic regression model variables

Model	Covariate (independent variable)	Dependent variable
1	Gender	Clozapine continuer or discontinuer
2	Age	
3	Ethnicity	
4	Diagnosis	
5	Length of clozapine delay	
6	Number of antipsychotics prior to clozapine	

I chose to enter gender as the first variable, as the *t*-test performed above showed a statistically significant difference between the number of male patients in the discontinuer

and continuer groups. The overall model summary statistics for each of the six models are shown below. The chi-square statistic is given for the overall model (in the row labelled 'model'), and for the change since the previous model (in the row labelled 'block'). The associated degrees of freedom are given in the next column, and the significance value for the test in the final column.

Table 6-4 Sequential binary logistic regression model summary statistics

		Chi-square	**df**	***p***
Model 1	Block	6.812	1	0.009
	Model	6.812	1	0.009
Model 2	Block	1.222	1	0.269
	Model	8.035	2	0.018
Model 3	Block	2.375	2	0.305
	Model	10.409	4	0.034
Model 4	Block	0.416	2	0.812
	Model	10.826	6	0.094
Model 5	Block	0.232	1	0.630
	Model	11.057	7	0.136
Model 6	Block	0.022	1	0.883
	Model	11.079	8	0.197

Table 6-4 shows that model 1 is a significant fit of the data, χ^2 (1) = 6.812, p = 0.009. Model 2 is a significant fit of the data, χ^2 (2) = 8.035, p = 0.018. Model 3 is a significant fit of the data, χ^2 (4) = 10.409, p = 0.034. Model 4 is a not a significant fit of the data, χ^2 (6) = 10.826, p = 0.094. Model 5 is not a significant fit of the data, χ^2 (7) = 11.057, p = 0.136. Model 6 is not a significant fit of the data, χ^2 (8) = 11.079, p = 0.197. However, no model is a significant improvement over model 1 (all block significances > 0.05), so adding each interaction term to the first has virtually no effect on the fit.

The binary logistic regression therefore shows that gender is the sole predictor variable that significantly contributes to the prediction of the outcome (continuing or discontinuing clozapine). Consequently, I went on to run the logistic regression with gender as the sole predictor variable. The iteration history for this model is shown in Appendix H (Table 7-245), and gives the -2*LL* (-2 log likelihood) as 173.954. The -2*LL* is the logistic regression equivalent of the residual sum of squares described earlier in this thesis in relation to multiple regression. It gives an indication of the amount of error in the categorical model by adding the probabilities associated with the predicted and actual outcomes. Large values for this

statistic therefore suggest a poorly fitting model, because the larger the 2 log likelihood, the more errors, or unexplained observation in the data, there are. The -2*LL* given in this output relates to the model before the gender variable was added (it is the baseline -2*LL*).

The summary statistics for the model are shown in the next table in Appendix H (Table 7-246). This shows the -2*LL* for the model after gender has been added as a predictor variable to be 167.134. The chi-square statistic for this model, calculated in the first model in the above regressions is 6.182, with a highly significant *p* of 0.009. This chi-square statistic is the difference between the baseline -2*LL* (173.954) and the current -2*LL* (167.134).

The classification table shown in Appendix H (Table 7-247) demonstrates that the model correctly classifies 85 patients as continuers (100%), but misclassifies zero patients as discontinuing when in fact, 48 did (0% accuracy). Overall, this gives the model accuracy for prediction of the outcome of 63.9%.

The Wald statistic is given in the next table in Appendix H (Table 7-248) as 6.100, with a significance of 0.014, indicating that gender is making a significant contribution to the prediction of continuing or discontinuing clozapine.

Earlier, I described Levene's test for the gender variable as being significant, meaning that equal variances should not be assumed. I have described the bootstrapping process that deals with this problem extensively in previous chapters. The bootstrapping results for the variables are given in Table 7-249 in Appendix H, and show the bootstrap re-estimates of the standard error. This changes the significance value for the *b* to *p* = 0.010 (from 0.021, and remaining significant). The bootstrap confidence interval indicates that the population value for *b* lies between 0.235 and 2.138, and since this interval does not include zero I can conclude that there is a genuine positive relationship between gender and continuing or discontinuing clozapine.

As described previously in relation to linear regression, the *R* value (the multiple correlation coefficient) gives a measure for how well the model fits the observed data. The *R* value is the correlation between the outcome variable and the predictor variable, and can vary

between -1 and 1. The *R* is calculated by taking the square root of the Wald statistic (6.100) minus twice the degrees of freedom for this statistic (2 x 1), divided by the baseline -2*LL* (173.947). The value of *R* is therefore 0.15.

This value cannot simply be squared to give the R^2 value described in this thesis when discussing linear regression, because as described above the *R* for logistic regression depends on the Wald statistic, which may be inaccurate when the regression coefficient *b* value is large (the standard error is increased in this circumstance, which results in an underestimation of the Wald statistic and a risk of a Type II error). Instead, I have calculated Hosmer and Lemeshow's measure (R^2_L) by taking away the -2*LL* of the model (167.134) from the baseline -2*LL* (173.947), then dividing by the -2*LL* of the baseline (173.947). This gives a value for R^2_L of 0.039. The model summary table presented earlier also gives two other measures of R^2; Cox and Snell's R^2 (0.05) and Nagelkerke's R^2 (0.068). These give slightly different values of R^2 but can all be used to provide a measure of the effect size of the model.

Table 7-248 in the Appendix also provides a value for the odds ratio (Exp(B)). This is calculated as the exponential of the *b* for the predictor variable ($e^{1.105}$), and is 3.019. This indicates that the odds of a patient who is male discontinuing clozapine is 3.019 times higher than those of a female patient discontinuing. The confidence intervals for this odds ratio are provided in the table as 1.256 – 7.255. As this interval does not contain 1, there is confidence that the direction of the relationship observed in the sample is true in the population; i.e. that as the predictor increases (more likely to be male), the odds of the outcome (clozapine discontinuation) also increases.

The table of residuals (the residuals are the differences between the values of the outcome predicted by the model and those observed in the sample) in Appendix H (Table 7-250) lists the expected probability of discontinuing clozapine based on the model. The only predictor of discontinuing clozapine that was included in the model was gender, and this was given a value of either 1 (male) or 0 (female). The probability values in the table are derived from using these values in the logistic regression equation, along with their respective regression

coefficients (*b*). The table shows that when a patient is male, there is a probability (shown as predicted probability of discontinuing) of 0.430 that they will discontinue clozapine (43% chance of discontinuing clozapine if the patient is male). For female patients, the probability of discontinuing is 0.2 (20% chance of discontinuing clozapine if the patient is female). This table also provides the residual statistics, which look for points where the model fits the data poorly, and points that exert undue influence on the model. In this way, the residuals provide an assessment of how well the model fits the data. Cook's distance looks for individual cases that influence the model, and any values for this statistic that are more than 1 indicate that that particular case is impacting on the model's ability to predict all the other cases. For this data set, all of the values for Cook's distance are less than 1. The leverage values, also shown in the table, are a gauge of the influence of the actual value of the outcome variable over the predicted values for the variable. The average leverage value is defined as the number of predictors in the model plus 1 (1 + 1) divided by the sample size (133), and is therefore 0.015. If no individual patients are exerting undue influence on the model, then all the leverage values should be close to this average, with a boundary of twice the average (0.03) requiring investigation, and three times the average (0.045) being a cut-off point. For this data set, the leverage values for all the cases are within the boundary of twice the average leverage. The normalised residual values are given in the next column. As the residuals represent the error associated with the model, when they are small the model is a good fit of the sample data. For standardised residuals, as presented here, the residuals are converted into *z*-scores (discussed previously in this thesis). In a normally distributed sample, only 5% of the residuals (or *z*-scores) should lie outside +/- 1.96, 1% should lie outside +/- 2.58, and none should be above 3. For these data, the standardised residuals for 8 cases lie outside +/- 1.96, which is equivalent to 6% of the total. None are outside the larger values. Finally, the DFBeta is the difference between a parameter that has been estimated using all the cases in the data set and that estimated when one case is excluded. It is therefore useful to identify cases that have a large influence on the parameters of the model. The DFBeta is calculated for each patient and the constant in the regression equation in the penultimate column, and each patient and the predictor variable (being male) in the

final column. Absolute values for either DFBeta that are above 1 indicate cases that substantially influence the model parameters; no values for these data are above 1. Overall, the model diagnostics suggest that the model is reliable and has not been influenced unduly by any subset of cases.

6.3.1.1 Binary logistic regression summary

The coefficients of the model predicting whether a patient discontinued clozapine [95% BCa bootstrap confidence intervals based on 1000 samples] are shown below in Table 6-5.

Table 6-5 Binary logistic regression model coefficients

		95% CI for odds ratio		
	b	**Lower**	**Odds**	**Upper**
Constant	-1.386 [-2.398, -0.694]			
Gender (male)	1.105* [0.235, 2.138]	1.256	3.019	7.255

Model χ^2 (1) = 6.812, p = 0.009.
* p =0.014

6.3.2 Survival analysis

The total sample included 133 patients; of these, 48 (36%) discontinued. The patients in this study can therefore be described as either 'surviving' to the end of the study (remaining on clozapine), or not surviving (discontinuing clozapine before the end of the study). However, the total study time was different for each patient. The follow up time for each patient in the study was the time from first clozapine use to the date of the end of the study (01.11.14), and therefore each patient had a different follow up time as start times differed. Each patient also had a different survival time (meaning the time from starting clozapine to the outcome event occurring – i.e. either discontinuation, or the end of the study if the patient did not discontinue clozapine).

6.3.2.1 Actuarial survival analysis

One option for reporting survival times for these data is to report the proportion of patients surviving at a fixed time point, e.g. At 1 year, 2 years, 3 years. This has the disadvantage of restricting the analysis to patients for whom complete information is available at the time point – i.e. some will be lost to follow up before completing the time period and will be

excluded from the analysis. If the time period studied is short, then any effect of time on the rate of occurrence of the event may not be seen – i.e. the rate of occurrence of discontinuation may not remain constant over time. It might be logical to expect the probably of discontinuing to be higher in the first year due to blood test frequency, and then to decrease over time as the blood monitoring burden reduces. Alternatively the probability of discontinuing may increase over time as the regular input from health care services forced by frequent blood testing decreases.

For this method of survival analysis, the starting point for each patient is the start date of the clozapine prescription, and the end point (a binary variable) is continuing or discontinuing clozapine. The calculated time between these two points is the survival time for the patient. All patients in the study had a survival time of at least 4 years, and so up to this point the probability of discontinuing is simply the number of patients that discontinued clozapine divided by the number of patients that continued clozapine. Naturally, the probability of continuing clozapine is therefore 1 minus the probability of discontinuing clozapine. The following probabilities can be calculated for the first 4 years using this method (see Table 6-6 below).

Table 6-6 Actuarial survival analysis, years 1 - 4

Within…	**Probability of discontinuing**	**Probability of continuing**
Year 1	12 / 133 = 0.09	1 – 0.09 = 0.91
Year 2	6 / 121 = 0.05	1 – 0.05 = 0.95
Year 3	7 / 115 = 0.06	1 – 0.06 = 0.94
Year 4	11 / 108 = 0.1	1 – 0.1 = 0.9

After year 4, some patients are lost to follow up for the later time periods because they entered the study too late to allow longer follow up times – i.e. they started clozapine in 2010. In order to calculate the probability of discontinuing in these time periods these patients who were effectively unable to complete the defined follow-up period must be accounted for (these patients are known as ‘censored’). This is done by estimating that on average, each censored patient was observed for half the follow up period without experiencing any discontinuation event. Therefore the probability of discontinuing during this interval is the

number of observed discontinuations divided by the size of the cohort minus half the losses due to censoring. In other words, censoring reduces the effective size of the cohort by half the size of the group lost to follow up. This is important as rather than removing them from the group entirely, the censored patients still contribute information to the overall probability of discontinuing.

For the years following year 4, the following probabilities can now be calculated, taking censored patients into account (Table 6-7).

Table 6-7 Actuarial survival analysis, years 5 - 8

Within…	**Effective size of cohort, accounting for censoring**	**Probability of discontinuing**	**Probability of continuing**
Year 5	97 – (0.5 x 3) = 95.5	4 / 95.5 = 0.04	1 – 0.04 = 0.96
Year 6	90 – (0.5 x 22) = 79	5 / 79 = 0.06	1 – 0.06 = 0.94
Year 7	63 – (0.5 x 19) = 53.5	3 / 53.5 = 0.06	1 – 0.06 = 0.94
Year 8	41 – (0.5 x 24) = 29	0 / 29 = 0	1 – 0 = 1.0
Year 9	17	0	1

The cumulative probabilities for discontinuing clozapine can be estimated by multiplying the probability of continuing clozapine in the previous year(s) by the probability of discontinuing in the current year. These are presented in Table 6-8 below.

Table 6-8 Actuarial survival analysis cumulative clozapine discontinuation probabilities

Year	**Calculation**	**Cumulative probability of discontinuing during this year**
1	N/A	0.09
2	0.91 x 0.05	0.05
3	0.91 x 0.95 x 0.06	0.05
4	0.91 x 0.95 x 0.94 x 0.10	0.08
5	0.91 x 0.95 x 0.94 x 0.90 x 0.04	0.03
6	0.91 x 0.95 x 0.94 x 0.90 x 0.96 x 0.06	0.04
7	.91 x 0.95 x 0.94 x 0.90 x 0.96 x 0.94 x 0.06	0.04
8	0.91 x 0.95 x 0.94 x 0.90 x 0.96 x 0.94 x 0.94 x 0	0.00
Probability of discontinuing clozapine at any point during the 9 year follow-up period = 0.38		
Cumulative survival probability for the cohort = 0.62		

Using the data calculated above, the actuarial life table can be constructed, with the corresponding life curve below in Table 6-9 and Figure 6-2 Actuarial life curve

Table 6-9 Actuarial life table

Year	Number at start of interval (*N*)	Number of discontinuations (D)	Number of losses to follow up (L)	Effective size of cohort (*N* – 0.5L)	Probability of discontinuing through the year (D/(*N*-0.5L))	Probability of continuing through the year (1 – D/(*N*-0.5L))	Cumulative survival
1	133	12	0	133	0.09	0.91	0.91
2	121	6	0	121	0.05	0.95	0.86
3	115	7	0	155	0.06	0.94	0.81
4	108	11	0	108	0.10	0.90	0.73
5	97	4	3	95.5	0.04	0.96	0.70
6	90	5	22	79	0.06	0.94	0.66
7	63	3	19	53.5	0.06	0.94	0.62
8	41	0	24	29	0.00	1.00	0.62
9	17	0	0	17	0.00	1.00	0.62

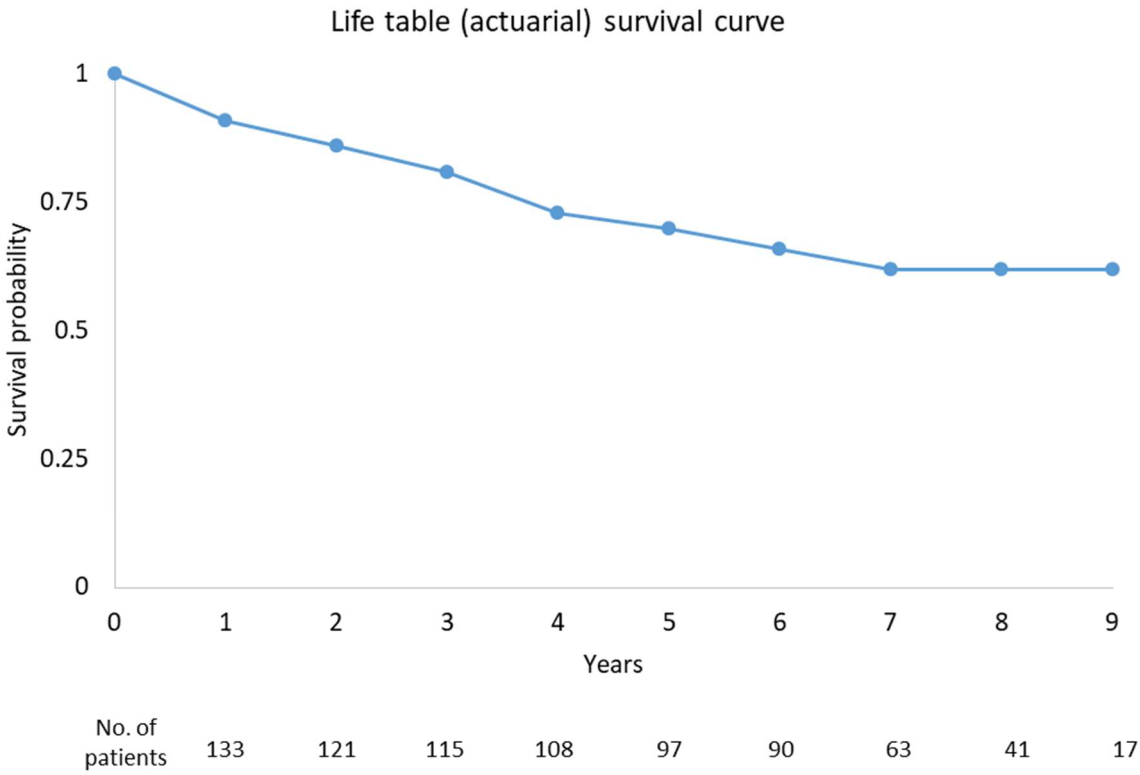

Figure 6-2 Actuarial life curve

6.3.2.2 Kaplan-Meier survival analysis

The actuarial method does not require information on the exact time at which discontinuations or censoring occurred. Only knowledge of the status of the patient at each of the limits of each time interval is required. Since these data include the exact times of discontinuation and censoring, survival probabilities can be estimated immediately after each patient's discontinuation event without the need to aggregate data into intervals of time. This method of survival analysis is the Kaplan-Meier method. The survival table for this method is given in Appendix H (Table 7-251), and shows each individual patient on a separate row of the table, in the order in which they discontinued clozapine or were censored from the study, along with the time point at which this occurred. From this table, the survival curve presented below can be constructed (Figure 6-3).

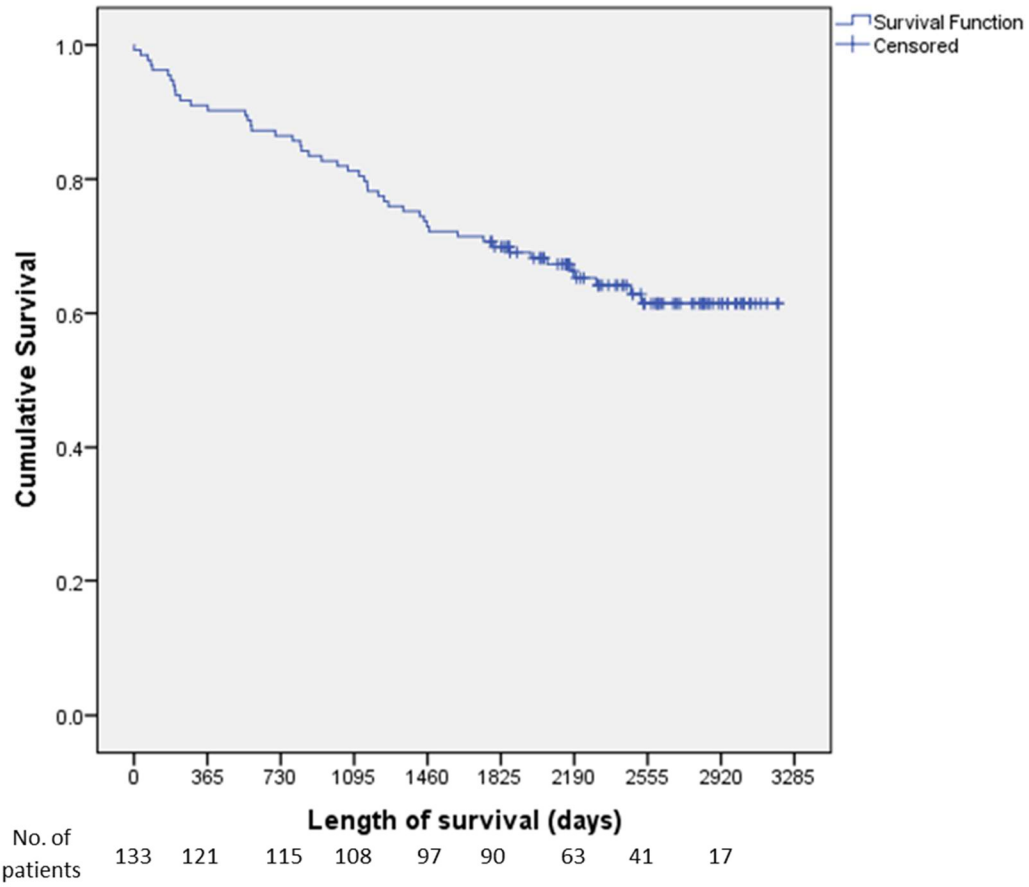

Figure 6-3 Kaplan-Meier survival curve, total patient cohort

The previous data analysis presented in this chapter suggested that male patients may be more likely to discontinue clozapine than females. I therefore completed the Kaplan-Meier survival analysis separately for males and females. A summary table of the cases is provided in Appendix H (Table 7-252), showing that of the 93 male patients, 40 discontinued clozapine at some point during the study, and 53 (57%) were censored. For the 40 female patients, 8 discontinued clozapine and 32 (80%) were censored. Overall, of the 133 cases, 48 discontinued and the remaining 85 were censored (63.9%). The corresponding survival table, differentiated for male and female patients is given in Appendix H (Table 7-253), and the Kaplan-Meier survival curve is below (Figure 6-4).

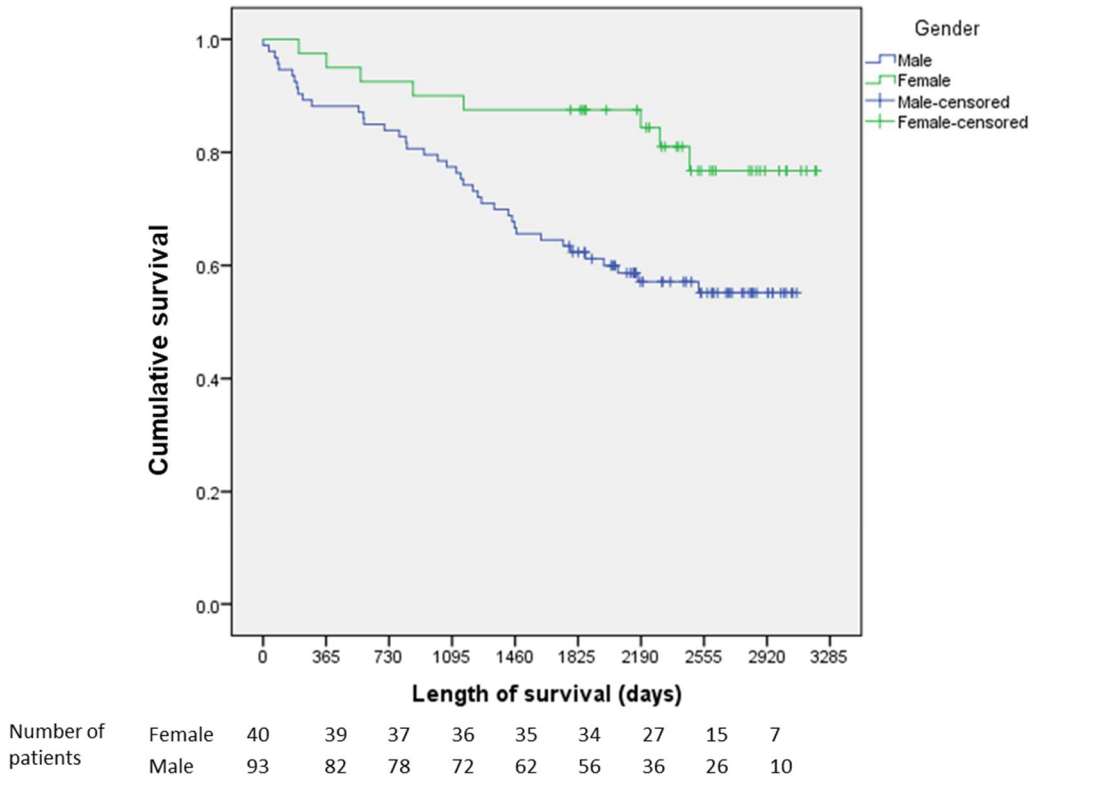

Figure 6-4 Kaplan-Meier survival curve, separated for gender

6.3.2.3 Relative risk

The risk estimate of discontinuing depending on being male or female can be calculated, and the table presented in Appendix H (Table 7-254) shows the risk estimate for male patients discontinuing to be 2.151, meaning that the risk of discontinuing clozapine if a patient is male is more than twice that if they are female. This is the same as calculating the relative risk of discontinuing from the numbers of patients in each group; the risk of a male patient discontinuing (the number of males that discontinued, 40, divided by the total male patients in the sample, 93) divided by the risk of a female patient discontinuing (the number of females that discontinued, 8, divided by the total number of females in the sample, 40). This calculates the relative risk of discontinuing for males versus females to be 2.15. The chi-square test associated with this risk estimate is also given in Appendix H (Table 7-255), and shows the significance value to be 0.011. Therefore there is a significant association between gender and whether a patient discontinued clozapine or not, χ^2 (1) = 6.421, p =

0.011. Based on the odds ratio, the risk of discontinuing clozapine was 2.15 times higher if a patient was male.

6.4 Summary

For the current analysis, 16 patients from the original cohort of 149 patients were excluded. Of the excluded patients, 5 had died between the end of the previous study and the end of the current analysis, 9 were lost to follow up (discharged out of the Trust), and 2 were excluded for other reasons (1 duplicate patient, 1 had received clozapine before the start date of the analysis). After exclusions, the study population consisted of 133 patients.

Of the study population of 133 patients, 48 discontinued clozapine at least once during the study period. Of these 48 discontinuers, 14 (29%) stopped permanently. The remaining 71% (34 patients) were eventually restarted on clozapine after failure of other treatments. Of these 34 patients, 24 remained on the clozapine, and 14 discontinued a second time. Of this cohort, 10 patients were restarted on clozapine for a third time following a break using non-clozapine antipsychotics, 4 patients stopped permanently. Of the 10 patients who restarted clozapine a third time, 4 discontinued again. Of these 4 patients, 2 were not restarted on clozapine, and 2 were rechallenged a fourth time. Both patients who started clozapine again after the fourth discontinuation stopped the clozapine again, both permanently this time. Patients who died during the study are reported separately. The mean time to clozapine discontinuation was 1032 days, with a range of 1 – 2524 days. The majority of discontinuing patients (75%) stopped clozapine within the first 4 years of treatment.

Clozapine discontinuers were more likely to be male ($t = 2.77$, $p = 0.007$). Based on the odds ratio, the odds of discontinuing clozapine were 2.15 (95% CI 1.1 – 4.2) times higher if a patient was male. There were no statistically significant differences between clozapine continuers and discontinuers in terms of their age when clozapine was first started ($t = 1.81$, $p = 0.072$), ethnicity ($\chi^2 = 4.62$, $p = 0.34$) or diagnosis ($\chi^2 = 0.012$, $p = 1.00$). Binary logistic regression found sequential models using individual variables as predictors to be non-significant for age ($\chi^2 = 1.22$, $p = 0.27$), ethnicity ($\chi^2 = 2.38$, $p = 0.31$), diagnosis ($\chi^2 = 0.42$,

p = 0.81), length of clozapine delay (χ^2 = 0.23, p = 0.63) and the number of antipsychotics used prior to clozapine (χ^2 = 0.02, p = 0.88), but significant for gender (χ^2 = 6.81, p = 0.009).

Most patients who discontinued clozapine (n = 34 of the total cohort of 48 discontinuers, 71%) stopped clozapine just once, with a further 10 patients (21%) stopping twice, 4 patients (8%) stopping three times and a further 2 patients (4%) stopping four times. After the first clozapine stop, most were switched to an oral (n = 39, 81%), atypical (n = 40, 83%) antipsychotic. Of these patients, the majority (n = 34, 71%) restarted clozapine. Over a quarter of discontinuing patients (n = 14, 29%) stopped clozapine at least twice during the study period, and following this second stop 71% (n = 10) restarted clozapine for a second time. After the second clozapine discontinuation, most patients were given depot antipsychotic treatment (n = 8, 57%). In total, 8% of patients (n = 4) stopped clozapine three times, and two of these patients were restarted after the third stop. Of these two patients, both stopped clozapine a fourth time, and neither were restarted after this fourth stop.

The most frequent drug switched to in the first instance was olanzapine (n = 13, 27%), followed by amisulpride (n = 10, 21%) and risperidone (n = 10, 21%). Other drugs chosen included aripiprazole, flupenthixol, haloperidol, quetiapine, zuclopenthixol, pipothazine, and a combination of aripiprazole and olanzapine. One patient was given no antipsychotic after clozapine was discontinued, as the diagnosis of schizophrenia was by that time uncertain. After a second discontinuation of clozapine, the medication chosen to switch to varied widely, with no clear majority for any particular drug (pipothiazine, flupenthixol, haloperidol, amisulpride, olanzapine, risperidone, paliperidone, zuclopenthixol were all presented).

The most common reason for discontinuing clozapine for the first time was patient refusal (n = 36, 75%). Where documented in the clinical notes, this was further specified as refusal of blood tests (n = 3, 6%) and refusal due to adverse effects (n = 4, 8%). No specific reason for treatment refusal was given for 29 patients (60%). Clozapine was stopped due to blood dyscrasia for 9 patients (19%), another medical reason for 2 patients (4%), and due to a change in diagnosis for one patient (2%).

At the end point of the study, 5 patients had died. Of these, 3 (60%) were taking clozapine at the time of death. For those taking clozapine, causes of death were suicide (*n* = 1), 'blood clots' (*n* = 1) and pneumonia (*n* = 1). The remaining two patients died following pulmonary embolism (*n* = 1) and 'collapse' (*n* = 1).

6.5 Publications arising from this study

See Appendix I: **Siobhan Gee**, Sukhwinder Shergill, David Taylor (2018) Long-term follow-up of clozapine prescribing. *Journal of Psychopharmacology*, online first

7 Discussion

This thesis examines prescribing of clozapine in an NHS Trust in South East London. I investigated the point at which clozapine was prescribed in a patient's treatment course, the reasons for prescribing (or non-prescribing) from the perspective of clinicians, the opinions of patients on starting clozapine, the consequences of prescribing later in a patient's illness, and the effects of discontinuing clozapine. An extensive retrospective case note review, a healthcare professional survey and a patient interview series were conducted, leading to publication of 5 original peer-reviewed journal articles.

Every patient's schizophrenia is different. The symptoms and their relative severity are different, the onset and illness course are different, and the effect of medications on these elements is different. Although the majority of patients will respond to one antipsychotic or another, it is clear that for about a third, the only antipsychotic that is effective is clozapine. This response to clozapine, or lack of response to other antipsychotics, is used to define the diagnostic subtype 'treatment-resistant' schizophrenia. Evidence from trials that show a lack of response to non-clozapine antipsychotics even in the first episode of illness (70) suggest that at least for some patients, treatment-resistance may be an inherent part of the condition from the start. The defining characteristic of this group of patients may be considered to be a response of symptoms to clozapine. As discussed earlier in this thesis, the common mode of action for all antipsychotics is blockade of dopamine receptors, specifically D2. For non-treatment-resistant patients, the degree of D2 blockade provided by antipsychotic medication broadly correlates with clinical response for non-clozapine antipsychotics (188). This does not appear to be the case for patients with treatment-resistant illnesses, where even maximum dopamine blockade does not alleviate symptoms (189). Correspondingly, dopamine blockade does not explain why clozapine is effective; where treatment-resistant patients are switched from a depot antipsychotic to clozapine, there is no delay in response to clozapine despite the depot still completely occupying dopamine receptors well after it has been stopped, and treatment switched to clozapine (190). Treatment-resistant patients appear therefore to have normal dopamine functioning (191), and clozapine is effective in

treating their symptoms through some other mechanism, possibly related to other neurotransmitters such as glutamate (192). Further support to the glutamate theory of clozapine action comes from the observation that treatment-responsive patients, healthy volunteers, and, crucially, clozapine-resistant patients, all appear to have normal levels of glutamate and glutamine in the putamen, whereas clozapine-responsive patients have elevated levels of these chemicals (193). This different mechanism of action for clozapine is important in relation to the questions raised and answered in this thesis, since the effect of delayed use may be different to that seen for other antipsychotics (such as in delayed treatment in the first episode of schizophrenia).

My first study characterised the point at which clozapine was introduced to patient's treatment plan, and found a mean of 3.93 years from the point of a theoretical 'treatment-resistant' schizophrenia diagnosis to receiving clozapine. This is an improvement on the previous finding in the same Trust of 5 years (71), but still illustrates prescribing practices falling far outside those recommended by evidence-based guidelines. Further to this, not only are patients receiving trials of multiple non-clozapine antipsychotics prior to clozapine (a mean of 5.6 antipsychotics, with a range of 1 – 20), but these antipsychotics are also often (in 34% of patients) being prescribed in supramaximal doses (both as monotherapy and polypharmacy).

My finding of an almost 4 year delay to clozapine with a wide range in time delays across the population sample is in common with a similar study conducted in 2013, also in England. Najim and colleagues found a 5 year delay to clozapine initiation in their retrospective chart review of outpatients on clozapine, with a range of 0.2 – 16.1 years (72). In Turkey, Ucok et al. found a shorter delay of 2.4 years (100). Both papers used the same criteria for calculation of theoretical delay to clozapine as in my research, and so it may be that the differences reflect different practices in other countries, or, as suggested by Ucok et al. on closer inspection of their data, a difference in speed of access to clozapine depending on the type of unit in which the patient was being treated. Other authors report total time to clozapine prescription – i.e. time from first presentation to psychiatric services until clozapine is started.

I found this to be a mean of 8.6 years in my patient group, a figure in keeping with those reported elsewhere. In a 2008 study patients in New Zealand experienced a mean of 9.7 years to clozapine initiation (66), although this had markedly reduced by 2014 to 5.3 years (73). A longer time delay of 11.8 years was calculated by Laker et al. in an English cohort in 1998 (109), and a shorter time again by reported by Harrison et al. in New Zealand in 2010 of just 2.8 years, albeit after an injection of government funding targeted at decreasing the time delay (99).

All these studies, including mine, calculated the 'theoretical' delay to clozapine as the time from the end of a six week period of being on a second antipsychotic, to starting clozapine. This strict definition of the point at which treatment-resistance occurs is taken from Kane's 1988 paper (20), and although not arbitrary (most treatment response to antipsychotics occurs within the first 6 weeks, if any positive effect is to be seen) it is a definition that will not adequately describe all clinical journeys. Time to response to antipsychotic treatment is variable, and it is possible that some patients may begin to respond after 6 weeks – and perhaps some clinicians choose longer medication trials for this reason before switching to clozapine. A trial of many years however seems somewhat unreasonable. Indeed, a meta-analysis conducted by Agid and colleagues demonstrated that the overall clinical improvement seen with antipsychotics is greatest in the first week of treatment, compared to later weeks (194). This result was repeated in a longer term 1 year study by Leucht et al. (195), where the reduction in overall psychotic symptoms was greatest in the first two weeks (accounting for 32% of the reduction), with an additional 12.5% in weeks 3 and 4, and the change in this first month being higher than that added in the subsequent 48 weeks of the first year of treatment. Even more strikingly, a study of acutely ill patients given fluphenazine found that those who failed to respond (defined as less than a 20% reduction in psychotic symptoms) in the first week were also guaranteed to remain non-responders by week 4 (196). It is also possible that some patients respond initially to a second antipsychotic trial, but then latterly 'become' treatment-resistant. If this were the case, a pattern of medication use of two antipsychotics prior to clozapine, with a long latency to clozapine starting would be expected. I did not find this; instead I found multiple antipsychotic trials being given, frequently in

combination and at higher doses than those licensed. This suggests non-response to these medication trials and a probable diagnosis of treatment-resistance much earlier in the illness than the introduction of clozapine would suggest, even if not at exactly 6 weeks after the second antipsychotic trial was started.

A further interesting observation from the pre-clozapine prescribing data presented in this thesis is the high proportion of what could be described, at least on initial inspection, as poor prescribing. In my study 34.2% of patients had supramaximal doses of antipsychotics prescribed – a practice that is unlicensed, in the case of monotherapy (representing 45.9% of the supramaximal doses), and lacking a clear evidence base in the case of both monotherapy and polypharmacy. It has long been the case that mortality is believed to increase with antipsychotic polypharmacy (197, 198), although more recent studies have failed to find this association (199, 200). A recent meta-analysis found polytherapy with antipsychotics more effective for prevention of rehospitalisation than monotherapy with all other oral antipsychotics, except for clozapine (201). Nonetheless, it is the case that pill burdens may be increased, side effects are inevitably increased or compounded, and so the rationale for this prescribing strategy is unclear. Presumably, prescribers see a lack of efficacy of the non-clozapine antipsychotics, prompting dose increases in the hope of also increasing efficacy, or combining non-clozapine antipsychotics with the same aim (and perhaps targeting different mechanisms of action). An alternative reasoning for the use of polypharmacy is an attempt to reduce side effects; if higher doses of one drug are intolerable, using a second may allow dose reduction of the first. Despite these arguments, trials have largely failed to find substantial benefits to either strategy, but the risks of high dose prescribing (polypharmacy increases the likelihood of this occurring), particularly to long term cardiovascular and metabolic health, are clear (202). Efforts have been made, both locally and nationally, to reduce high dose prescribing (145), and the use of polypharmacy had reduced from 65% in the same hospital Trust in 2003 (71) to 54% in the current study. Nonetheless, my data show that these undesirable prescribing practices persist.

Surprisingly, the number of inadequate antipsychotic trials pre-clozapine was also high in my sample (70.5% of patients). The definition of an 'inadequate' trial is of course somewhat artificial – each patient will respond differently in terms of doses that are either effective or tolerated – but despite this, the number of inadequate trials prescribed is considerable. Of these, 41% were due to a prescribing duration of less than 6 weeks – this may be reasonable and unavoidable if the patient cannot or will not tolerate a 6 week trial due to side effects. Underdosing occurred in 33.6% of the inadequate trials, again possibly reasonable since the 'minimum effective dose' will naturally be lower than the average for some. It is also possible that prescribing was unintentionally inadequate – that is, clinicians were simply unaware of the commonly accepted minimally effective doses, or that 6 weeks is generally suggested as a minimum time course to assess effectiveness. However, both recommendations are freely available in local prescribing guidelines. It also seems illogical that for patients not responding to an antipsychotic (as was eventually the case for all the patients in the cohort, as they were all finally given clozapine) doses were not increased. It is conceivable that for patients who were highly symptomatic, six weeks was perhaps too long to wait for response – an understandable pressure to do something other than simply waiting in the face of continued symptomatology may be a factor. Overall one can envisage many different clinical scenarios that would explain my finding of such a high frequency of inadequate antipsychotic trials. To the best of my knowledge no other authors have studied the prevalence of inadequate prescribing in this way in naturalistic samples.

Within the Trust, approximately 350 patients present with new onset schizophrenia each year. Of these, one third (117 patients) can be expected to be treatment-resistant. Yet less than half that number (just 50 patients) start clozapine each year. Unfortunately, and as previously described, this is not unusual, either within the UK (80) or internationally (52, 63). The most recent comprehensive UK survey of prescribing in schizophrenia (the National Audit of Schizophrenia (203)) reported 23.7% of patients to be prescribed clozapine, with high variations between Trusts. Of the sample studied, 40% of patients appeared to be treatment-resistant and eligible for clozapine, but were not prescribed it. In the most part,

this thesis therefore describes a cohort of patients with treatment-resistant schizophrenia who are unusual in their peer group, in that they received clozapine to treat their illness.

I found female patients experienced a longer delay to clozapine initiation. Alessi-Severini and colleagues found women had a shorter length of therapy prior to clozapine (7.7 years, compared to 8.9 years in men) (59), but most other authors found clozapine users more likely to be male (52-54, 75, 76) or for there to be no difference in prescribing prevalence between genders (67, 77, 204). An increased proportion of men in clozapine-receiving populations does not necessarily mean a longer delay to clozapine for women, as the risk of developing schizophrenia is higher for men (205). It has been suggested that men suffer a more severe illness course than women (54), which may explain the shorter time course to clozapine in my group, if prescribers are more likely to reserve clozapine for their most ill patients. Nielsen and colleagues found that in their cohort of clozapine patients, women had been given more non-clozapine antipsychotics in the period before clozapine started than men, and had also had more hospital admissions and inpatient bed days in this period, suggesting a higher illness burden (63). They did not however find any statistically significant difference in the prevalence of clozapine prescribing between the genders. Although I did not gather illness severity data for my cohort, all patients experiencing a treatment delay to clozapine initiation were, by definition, eligible to receive clozapine, regardless of symptom burden. It is possible that female patients were eligible to start clozapine, but their prescribers deemed their symptoms not severe enough to warrant clozapine. There may be other reasons – perhaps female patients are considered more likely to be non-compliant with clozapine and/or concurrent blood testing. Concerns around prescribing of clozapine to women of child-bearing age may also play a part. It may be that female patients are offered clozapine but are more likely to refuse. Other authors have found women to be less adherent to medication regimens than men (206, 207), although where this has been studied in patients with schizophrenia, no differences between the genders have been demonstrated in terms of antipsychotic compliance (208, 209). If females have a higher burden of co-morbid medical conditions this may also limit clozapine prescribing.

I did not find an interaction effect of age on the delay to clozapine use, once illness duration was controlled for. Older age has been associated with a longer delay by several other groups (71, 72), as has duration of illness (72). Illness duration is of particular relevance as clozapine was only made available in the UK in 1990, and so for some patients clozapine may not have been available in the earlier stages of their illnesses. The finding by other groups of a longer delay to clozapine use in older patients may be partly explained by prescribers being less likely to readily consider clozapine for patients who have more comorbid physical illnesses, which is more likely in those who are older. It has also been suggested that younger patients are more likely to be treated robustly more quickly, as the drive to reduce a long term symptom burden with associated social deficits may be felt more urgently in younger patients. In my clinical experience, some prescribers also express a view that patients who have been unwell for long periods of time are less likely to respond to medication, reducing confidence in clozapine being effective in older patients. This assumption is investigated in this thesis. It is encouraging that at this Trust, older patients do not appear to be treated differently from their younger counterparts.

I also found no effect of diagnosis or ethnicity on clozapine delay. Many other groups have demonstrated a higher representation of Caucasian patients in clozapine cohorts (53, 54, 77). Patients of African-American heritage may find access to clozapine more challenging as the presence of Benign Ethnic Neutropaenia (BEN) is more likely, and other authors have suggested that cultural factors also have an effect on prescribing in this group (54). It is reassuring that I found neither race nor diagnosis affected delays in prescribing. This may partly reflect the ethnic mix at this Trust; the population it serves in South East London has one of the highest proportion of Black patients in the UK (182).

An obvious reason for delay in prescribing clozapine is a lack of knowledge of the relevant guidelines (71). This seems unlikely to be the case for my cohort, since the NICE guidelines for schizophrenia (which specify the prescribing of clozapine in treatment-resistant schizophrenia) have been widely available, and unchanged in this regard, for more than a decade. A lack of familiarity with clozapine itself may be more likely – it is a drug with unique

monitoring requirements, both at baseline and in the long term. This theory is supported by evidence of wide variation in prescribing rates of clozapine within (75) and between Trusts (57, 58, 62, 78, 80, 81, 203). Prescribing seems to beget prescribing, with high volume prescribers (of any psychotropic) more likely to prescribe clozapine in a large study in the USA (81). Better support structures for prescribers, in the form of better access to general practice and more community care options were linked with higher clozapine prescribing rates in France (62). A lack of knowledge and confidence, especially in younger prescribers in outpatient settings appear likely to reduce prescribing of a complex drug (204), suggesting a need for not only staff education (62, 75, 81, 204) but also administrative support (54, 81, 210). Finally, patients themselves are frequently considered a barrier to prescribing, usually due to clinician fears of non-compliance either with the medication itself or the attendant blood tests (53, 71, 82).

I surveyed staff members to establish their opinions of clozapine, its efficacy, initiation, and factors that might help to reduce barriers to prescribing. Two methods were considered for doing this; face-to-face interviews, and self-administered questionnaires. The Trust employs 4600 staff across four London boroughs and so researcher-administered interviews or questionnaires were considered impractical. Additionally, the target population consists of any member of clinical staff who may be involved in clozapine treatment in any way – including influencing of patient opinions as well as directly prescribing. This therefore presents a widely heterogeneous population, including health care assistants, nurses, doctors, pharmacists, psychologists, social workers, occupational therapists and so on. This heterogeneity necessitated a large sample size in order to increase precision and reduce sampling error. Self-administered questionnaires allowed me to target the largest possible population, and had the additional benefit of being free from interviewer effects or variability. It is possible that being asked questions about medication by a Trust pharmacist would have elicited different responses than those given anonymously, especially from prescribers who may have felt obliged to give the ‘approved’ guideline-driven answers.

The questionnaire used in this study aimed to investigate four main themes that may contribute to a delay and/or under prescription of clozapine in treatment-resistant schizophrenia. These themes were identified from the clinical experience of the research team, feedback from the pilot questionnaire, and review of the relevant literature. These were: (i) a lack of knowledge of the guidelines and associated evidence supporting the use of clozapine as a third-line antipsychotic, and/or a personal lack of confidence in the effectiveness of clozapine when compared to other antipsychotics; (ii) patient reluctance to take tablets or agree to blood testing; (iii) psychiatrist concerns about future compliance or the development of side effects; and (iv) administrative hurdles to prescribing.

Doubts about the efficacy of clozapine were suggested as a barrier to prescribing by Taylor et al. in 2003 (71), and Downs and colleagues (80) felt that the publication of prescribing guidelines for clozapine contributed to increased prescribing rates in their review of English NHS Trusts. In Swinton et al.'s 1999 case note review and interview of forensic patients eligible for, but not prescribed clozapine (82), three quarters of the patients interviewed stated an unwillingness to comply with blood testing. Doctors asked in the same study also cited the likelihood of refusal of blood tests or the drug itself, either immediately or on discharge, as a reason for not prescribing. Patient reluctance to take tablets or agree to blood testing, and psychiatrist concerns about future compliance with therapy were also suggested by Taylor and colleagues (71) as reasons for the delay they found in clozapine prescribing in a cohort of treatment-resistant patients with schizophrenia in South East London. A further theme was that of administrative hurdles presenting barriers to prescribing in a variety of ways. A lack of staff to take blood samples was suggested by Swinton (82) as a reason for non-prescription of clozapine. Taylor (71) proposed that prescriber as well as patient fears about haemotoxicity or other side effects may affect prescription rates. The cost of clozapine prescribing was also put forward as a barrier. An increase in available funding to support clozapine initiation was given by Wheeler and colleagues as a way to increase prescribing rates in their 2008 retrospective chart review of patients with psychosis in New Zealand (66).

My study found that most practitioners who are directly involved in patient care considered themselves familiar with guidelines relating to the prescribing of clozapine, and felt that clozapine was an effective drug choice for patients with treatment-resistant schizophrenia. It is surprising that this claimed familiarity is not reflected in actual prescribing patterns within this Trust (148). Various explanations have been suggested (82, 127, 128, 211-213), but to my knowledge this is the first study to ask practitioners who are involved in prescribing decisions directly about their reasons for non-prescribing of clozapine. Unfamiliarity with the guidelines had been suggested as an obvious reason for non-adherence (63, 211), but here I have found that the majority of practitioners report familiarity with the guidelines, indicating this does not appear to explain non-adherence among practitioners in my study.

Historically, clozapine could only be initiated during a hospital admission. This is no longer the case, and starting clozapine in the community setting has been shown to be safe and effective (212, 213). In the past, concerns have been raised about the high resource burden this places on community teams (twice daily monitoring of vital signs is usually recommended for the first 7 – 14 days) (213). My survey suggests practitioners perceive this to be an on-going problem, with a majority indicating that dedicating community staff members, or creating day hospital beds specifically to support clozapine initiation would be a positive step. This would involve an up-front cost but, but balanced against the potential for clozapine to reduce relapse (85) might result in long term savings. The idea of dedicating staff members in the community to clozapine initiation has been trialled locally. A psychiatrist-led clinic assessed patients with treatment-resistant schizophrenia for clozapine initiation (or other interventions as appropriate), and demonstrated a five-fold increase in community-based clozapine initiation (214), although the cost-effectiveness of the service has not yet been evaluated.

A common theme in my survey was that of patients themselves being the reason for non-prescription of clozapine – either refusing to comply with the necessary blood tests, or else being unwilling to try a medication associated with so many side effects. When patients taking clozapine are asked directly for their views on it however, the vast majority are positive,

despite the obvious inconveniences (97, 135, 150). However, these surveys have been limited to the opinions of patients already taking clozapine. Perhaps the results of these, coupled with the results of my survey, suggest that counselling of prospective clozapine patients by those already taking clozapine might be more focussed on patient needs than the current, professional-led model.

Potential non-compliance with oral therapy was also a concern identified in my study. Not taking medication in the way in which it was prescribed is certainly not exclusive to psychiatry. Concordance with prescribing regimens tends to be at its lowest when the condition being treated is chronic, the medication prescribed is prophylactic (or viewed as such by the patient), and the consequences of stopping the medicine are delayed (215). Ensuring concordance for patients with psychosis does however have some specific challenges, perhaps most obviously a lack of insight into the illness which often accompanies psychotic symptoms, leading (naturally) to a refusal to take medication. Insight can fluctuate throughout the illness course, and is not always associated with non-compliance; it is not unusual for patients who are adamant there is nothing wrong with them to nonetheless continue to take medication for their (to them, non-existent) illness. Equally, a lack of what might be termed insight into the need for treatment is not exclusively the experience of patients with psychiatric illnesses – health beliefs around pharmaceutical medicines being harmful or unnatural, or that medicines should only be taken if you are sick (and not prophylactically) abound in those with physical health illnesses as well. There are of course other consequences of psychotic illnesses that may make regular medication compliance difficult, not least the distractibility and disorganisation that often accompanies active psychotic symptoms. Indeed, an increase in psychopathology has been shown to reduce medication compliance levels (215). Patients with mental illnesses are also more likely to abuse substances, which in turn increases the likelihood of non-compliance (215). A further factor which affects the chances of medication concordance is the acceptability of the medication itself; or conversely, the level of discomfort the patient experiences from the medication. A treatment that is ineffective, leaving the patient with unpleasant symptoms, is unlikely to be something the patient will wish to take regularly. The presence of side effects

is also more likely to lead to medicine refusal or non-compliance. In their study of 84 patients, Van Putten et al. found 46% to be at least partially non-compliant, and the likelihood of non-compliance was associated with the presence of EPSEs (216). A further consideration is the trust that patients put in their prescribing psychiatrist – it is often the case that different psychiatrists recommend different treatments for similar cases, and this does not go unnoticed by patients. An increasing level of mistrust in prescribing decisions is likely to lead to increasing levels of non-compliance (125).

Measuring the extent of non-compliance is challenging. In a study of 82 patients with glaucoma, doses of eye drops that were self-administered at home by patients were measured using an electronic device (217). The patients themselves were asked how many doses they missed, and they consistently underestimated; the proportion of missed doses was actually up to three times higher than that reported by the patients themselves. Even more strikingly, when their prescribing ophthalmologists were asked to estimate the degree of their patient's non-compliance, the doctors were completely inaccurate, with their estimates being no better than random. This inability of the prescriber to assess compliance is also the case in psychiatry. McClellan and colleagues tested medication levels in the urine of 286 patients, finding that 8% were actually taking no medication at all, and almost a quarter were taking less than they were prescribed (218). When the psychiatrists doing the prescribing were interviewed, their predictions of compliance in their patients were wrong in 20% of cases, with 29% thinking their patient was taking the medication, when they weren't, and perhaps even more surprisingly, 71% thinking their patient wasn't taking the medication, when they were. As well as using electronic devices and measuring drug levels in urine, compliance can also be assessed using pill counts and prescription refills. The former does not guarantee where the pill went after it was removed from the packet, and of course the latter also does not prove that the patient isn't simply stockpiling medication at home. A review of published reports using all these strategies suggested that overall compliance with antipsychotics averages about 58%, with a range of 24 – 90% (219). Patient interviews are generally a less accurate way of assessing compliance, and clinicians usually assess their patients as more likely to be taking the medication than they really are (the same study found

prescribers to think that on average patients are 72% compliant with antipsychotic medication).

Focussing on clozapine, fear of non-compliance has been identified previously as a barrier to prescribing (82, 220), although compliance with clozapine is actually better compared with other antipsychotics (118, 221). Recent data show that rehospitalisation rates for patients receiving depot medication are higher than those receiving clozapine (222), suggesting that the alternatives which guarantee compliance may still be worse for patient outcomes. Interestingly, in my study of pre-clozapine prescribing choices 57% of patients had been prescribed a depot medication. Although it cannot be assumed that this is due to non-compliance with oral medication in all cases, it might suggest that not taking tablets was not a significant concern for at least 43% of my cohort. It may instead be the case that non-compliance with blood tests is more of a concern than non-compliance with the medication itself. Clozapine does have the advantage over some other antipsychotics of having a readily available plasma level assay, and of course the patient is already subject to regular blood tests during which, presumably, plasma concentrations could also be checked to assure compliance. This doesn't seem to provide any immunity from the inability of prescribers to tell whether their patients are taking the medication or not; in a large review of clozapine plasma concentrations sent to a London pathology laboratory, no clozapine was detected in 1.5% of samples, despite these patients being prescribed doses up to 900mg (223).

The introduction of strict blood count monitoring reduced the incidence of clozapine-induced agranulocytosis to 0.38% from 1 – 2% - a saving of an estimated 137 lives over a 5 year period in a review of the monitoring system in the USA (224). The monitoring of full blood counts for patients receiving clozapine has therefore not only allowed this medication to be made available again to patients who otherwise had no other evidence-based treatment options, it has also probably prevented a considerable number of deaths worldwide. Whilst this is undeniably positive, I have shown that the blood tests themselves may also prevent patients from accessing clozapine, either because the idea of regular testing is unacceptable, or more directly because the rigid parameters within which the levels of white cells must fall

exclude otherwise treatment-adherent patients from therapy. This may occur due to the presence of BEN, which the monitoring guidelines attempt to adjust for, or due to other factors. Other medications may affect white cell counts, as may co-morbid medical conditions or external factors. Patients returning plasma levels of white blood cells outside of the acceptable ranges for these reasons are not necessarily at any increased risk of clozapine-induced agranulocytosis, but due to the licensing restrictions may nonetheless be barred from clozapine treatment.

Additionally, long term testing may be significantly off-putting for patients. Monitoring of white cell counts is mandatory on a monthly basis after the first year of treatment (during which it is more frequent) for the entire time the patient is taking clozapine, despite the fact that the risk of clozapine-induced agranulocytosis is reduced by this point to being no higher than that with any other antipsychotic, or indeed death from other causes, such as road traffic accidents (225). Consequently, there is a call from some practitioners to relax the blood monitoring rules since they are seen as an unnecessary, costly, and time-consuming activity. Evidence that doing so may increase clozapine acceptability is provided by countries that do not have such strict monitoring requirements; 71% of Icelandic patients (where the remote nature of parts of the country makes frequent blood testing sometimes impossible) taking clozapine remained compliant with therapy for 20 years, although overall use in the country remains below optimal levels (11% of all patients with schizophrenia) (226). Prescribing rates in China, where blood testing is recommended but not mandatory, are much higher, although other factors may also influence the choice of clozapine as a first-line treatment (91). Extremely strict blood monitoring policies have been blamed in part for the very low levels of clozapine use in Japan (52), but prescribing rates in Columbia, where clozapine prescribing is not restricted to treatment-resistant cases and is not bound by blood monitoring rules, are comparable to countries where restrictions are in place (52). Detailed economic analysis of strict monitoring protocols for clozapine has shown these also lack cost-effectiveness (227), with very small benefits in quality-adjusted survival (less than 1 day per patient) coming from not only high monetary costs, but also, as I have shown, costs to the likelihood of establishing patients on clozapine in the first place. Also of importance is consideration of the risk of harm

to the patient of not starting clozapine – taking clozapine reduces mortality from suicide (228). It is worth noting a counter-argument here – that the increased patient-clinician contact that arises from the compulsory blood testing is actually beneficial in reducing psychotic relapse, as earlier detection and intervention may be possible (229).

One way of improving the acceptability of blood sampling for clozapine may be to move from venous blood sampling to capillary sampling. Point of care testing (POCT) devices allow capillary sampling of the Full Blood Count (FBC) in the clinic or in the patient's home, returning a result whilst the patient is present, and allowing medication dispensing all within the same consultation. The current system of venous sampling requires attendance at a blood testing appointment, which may be at a different location to the psychiatric clinic (commonly the local acute hospital), waiting for the blood test results to be made available to the dispensing pharmacist (usually a few days), then for the patient to attend the psychiatric clinic to pick up their clozapine. Simplifying this process may make this easier to comply with. POCT devices are used in other settings for rapid diagnosis of malaria and HIV (230), and although some concerns have been raised (poor finger prick technique, sampling site, and the nature of capillary blood itself have all be shown to reduce the reliability of results), it has been used successfully for clozapine monitoring. Nielsen and colleagues describe a cross-over study comparing venous and capillary sampling for patients taking clozapine, with patients reporting POCT to be less painful and more convenient, and 63% of patients and 87% of clinicians finding it preferable to traditional venous testing (231).

The difference in opinions between professional groups is an important finding of this survey of practitioner attitudes to clozapine initiation. In my experience, prescribing is often a multidisciplinary decision. My study suggests that pharmacists tend to be both more confident in the practice of prescribing clozapine, and also in its potential benefits. As a result, the presence of pharmacists at the point of prescribing decisions may presumably increase the likelihood of clozapine being prescribed, and so a greater number and availability of pharmacists in organisations could improve clozapine prescribing patterns. There is increasing recognition of the importance of access to specialist pharmacists (10,

123). Educational and practical support from colleagues more experienced in the use of clozapine has been shown in New York state to increase clozapine prescribing rates (232), suggesting a positive influence of readily accessible advice from more confident co-workers.

It has been shown repeatedly that simply publishing guidelines intended to improve patient care does not, in fact, do so (131, 133, 233). Local education, audit and feedback are effective (75, 126) but the long term impact of these has not been evaluated. It seems that, at least locally, a lack of knowledge of the guidelines is not the barrier to prescribing, and so further education is presumably not the solution. My survey suggests that further investment is needed in services designed to initiate clozapine treatment in the community. Allowing organisational factors to delay or prevent initiation of the most effective medication for treatment resistant schizophrenia is clinically unacceptable. It is also potentially economically wasteful (90). Practitioners in my study showed concern over patient refusal of treatment, primarily due to tolerability or blood tests. Patient surveys suggest that these concerns may be inflated (97, 135, 150), and practitioners should be mindful of avoiding allowing their own perceptions of future treatment acceptability to influence prescribing.

Overall, this survey shows that practitioners know when and how to prescribe clozapine. Their barriers to prescribing are patient focussed – concerns about tolerability, co-morbid medical problems, compliance, or refusal to comply with blood test monitoring. The presence of staff members motivated to help patients make informed decisions about drug therapy, appears to be a key factor in increasing access to clozapine. Healthcare professionals know that clozapine is an effective medication, and they also know that a significant proportion of the patients under their care should be receiving it, where they are not. What halts the movement of pen to prescription pad are patient-led issues – potential, perceived, or real. No other study has attempted to examine these issues by asking the opinions of patients themselves – specifically patients who are eligible to take clozapine, but are not doing so.

I conducted a survey that aimed to evaluate and categorise the opinions of potential clozapine patients about clozapine initiation, its side effects and potential effectiveness. The patients included were specifically selected as those who were not taking, and had not ever,

taken clozapine previously, and who were also acutely unwell. This group of patients were considered to reflect most accurately those that clinicians might expect to treat in daily practice and for whom clozapine should be considered the treatment of choice.

Three methods for questionnaire administration were considered. Firstly, self-administration was deliberated. This has the advantages of being quick and cheap in terms of research-investigator time and input, and so may be able to attempt to reach a larger sample. It would also avoid interviewer bias and be convenient for responders, allowing patients to complete the questionnaire at a time of their choosing. However, this method is associated with a high chance of non-response or incomplete responses. Importantly, the nature of the population being studied (actively psychotic patients) would limit the types of questions and number of questions that could be included in a survey where no explanation of questions would be possible. It would also be likely to result in a biased return of responses, because presumably patients who are more unwell, less able to concentrate, have a poor understanding of written English or a learning disability are less likely to attempt or complete the survey. It would also be impossible to quantify the reasons behind non-response in this method. No prompting or probing with follow up questions would be possible, and it could not be guaranteed that the intended recipient actually provided the responses. In terms of question design, only questions highly salient to the patient would be possible otherwise the risk of non-response would be increased, and for the same reason the opportunity for use of open questions would be limited. Additionally no control over the order in which the questions would be answered would be possible.

Interviewer-administered questionnaires avoid many of these pitfalls, ensuring robust answers and also allowing for a higher number and more complex questions to be asked. A higher return rate is likely, and the reasons for non-response or exclusion from the study can be recorded. In this way a better quantification of potential bias (exclusion of those with poor or no English, concentration problems, comprehension problems and so on) would be possible. However, this type of data collection is not anonymous, even though analysis would be, and this may be off-putting to some participants. It is open to interviewer bias and

is time consuming. The most robust method for this type of survey is to use a structure laying technique, following up patients in the weeks after the initial interview in order to allow communicative validation of the content of the statements gathered, but this was felt to be impossible to complete given the nature of the clinical journey of patients through the hospital and into the community. Additionally the focus of the study was to investigate patient opinions at the time of medication change, i.e. when a new medication (clozapine) is likely to be considered, which is assumed to be early in admission. Patient opinions may change as the acute mental health crisis that necessitated admission resolves.

Finally, data gathering from clinical notes was considered. This has the clear advantage of being able to capture the complete sample, with no patients lost due to being transferred to different wards, or otherwise engaged in other activities making them impossible to interview. This is also likely to represent the least sample-biased option, as it avoids patients being unable or unwilling to fill in a questionnaire. However, I have found previously that documentation of medication decision-making in clinical notes is usually poor, and the results from this type of study would rely on good note-making around offering clozapine and the reasons for refusal. The results would also therefore be open to bias as any reason for refusal is documented by the doctor who offered the drug. Additionally any decision by the prescriber to not offer clozapine based on assumptions of patient-related barriers to clozapine treatment provides data related to the prescriber decision rather than that of the patient. In terms of patient opinions, it therefore would not capture data relating to patients who are eligible for but are not offered clozapine.

After review of options, interviewer-administered questionnaires were felt to be the most appropriate method. Question design was carefully considered. As much as possible, yes/no questions were used as these have a greater reliability than frequency scales in people with mental health difficulties (151). Finlay et al. (151) also suggest that cognitive impairment predisposes to response bias and social desirability, with participants responding to the topic rather than the particular question, or ‘yea saying’ which introduces systemic acquiescence bias. The latter can be improved by avoiding yes/no questions and instead

introducing either/or options, but Finlay warns this may increase the risk of last choice responding. Ideally, the validity of responses should be demonstrated using nonsense questions or pairs of reverse worded questions in order to measure acquiescence, but this may lead to confusion in my patient cohort, and also create long questionnaires which are unlikely to be completed by patients for whom a lack of concentration is part of their psychotic illness. The questionnaire used, along with the Likert scales used as visual aids for interviewees, is included in Appendix E.

A significant proportion of patients interviewed in this survey (46%) reported that they had never heard of clozapine, and 70% said they had never been asked to take it. I did not interrogate the clinical notes to establish whether this was the case, and arguably patients cannot be expected to recall all medicines that have been discussed with them in the past, but the lack of awareness by patients of the drug is striking and may be relevant to the low prescription rates of clozapine in this Trust (148). Conversely, this lack of familiarity may be seen as encouraging, as patients do not necessarily enter into a conversation about clozapine with preconceived ideas about its benefits or disadvantages. Further to this, 46% of patients stated that they would either take clozapine were it to be offered to them, or that they were unsure. A minority (35%) rejected the idea outright.

I found in my survey of health care professionals that clinicians consider patients' refusal to undergo blood tests to be the main barrier to prescribing of clozapine (149). In this study of patient opinions, a high degree of concern was expressed by some patients about this, with 36% of participants stating that blood tests would put them off trying clozapine. However, this proportion does not represent the majority – the remainder felt that the blood tests presented no worry at all (31%) or that they would be worried only to some extent, but still willing to try clozapine (30%). Thus for 61% of patients eligible for clozapine, blood testing was not a barrier to its use.

Also in my previous study, clinicians felt that the next most worrying aspect of clozapine therapy for patients was overall tolerability. I found 43% of patients to be unwilling to try

clozapine because of adverse effects, although again the majority were either not worried at all, or worried but still open to considering treatment (53%).

When considering hospital admission as a barrier to patients willingly accepting clozapine treatment, 49% of patients stated that this would mean they would not want to try the medication. Of the remaining patients, almost a third (29%) did not feel this was a concern at all, and this was further reflected in a similar percentage actively wishing to be in hospital rather than at home to start clozapine (26%). Therefore the main barrier to using clozapine in this cohort of patients is not blood testing but the apparent necessity to be admitted to start clozapine.

Finally, patients did not appear to consider clozapine to be as effective as the available data suggest it is, with 38% thinking it would be less helpful than other medicines they have taken previously, or were taking at the time of the study, just 24% thinking it would be better, and 12% considering it to be about the same. It is possible that patients were taking into account the burden of side effects, hospital admission and blood monitoring when answering this question – and this perhaps makes it all the more relevant. Nonetheless, educating patients about the potential benefits of clozapine is likely to prove beneficial in the attempt to get more people on to clozapine.

To my knowledge, this is the first study to evaluate opinions about clozapine of patients who are not taking the drug, but who, in accordance with local and national guidelines (234, 235), should be doing so. Further, this is the only study to ask patients about clozapine at a time of acute psychiatric relapse, the point at which treatment changes are most likely to be considered in 'real life'. Other authors have described the attitudes of patients who have already been established on clozapine, and these are overwhelmingly positive. Patients were repeatedly found not to mind the blood monitoring (94, 150), to prefer clozapine to their previous medications (94, 96, 236), and to find it generally helpful for them when compared to other medicines – even when they were considered to lack insight into their condition (93). These studies cannot be said to represent the views of patients who are not taking clozapine, and therefore cannot help to address the issue of chronic under prescribing of the medication.

My results do not show that patients are universally against the idea of clozapine, but that concerns about hospital admission (49% of patients wouldn't try clozapine because of this), adverse effects (43%) and, to a lesser extent, blood monitoring (41%) are important. These concerns do not apply to every patient however, and patients vary in the degree to which they express concern about these facets of treatment. A reluctance to be admitted to hospital in order to start a medication is understandable. Of course, medication changes are often prompted by psychiatric relapse, and so hospital admission may be necessary for reasons beyond purely medication initiation, and this aspect is not reflected in my survey. Nonetheless, avoiding hospital admission where possible is desirable not only for patients (although it should be noted that a significant proportion of patients in this survey expressed a wish to be in the perceived safety of the hospital environment when starting new medication), but also for NHS Trusts under pressure from a lack of available inpatient beds. As discussed previously, resources specifically targeted at enabling community-based clozapine titration may be helpful (214), a process that has been shown to be both safe and effective (237).

The adverse effects of clozapine are concerning to both clinicians and patients, as demonstrated by both surveys. Whilst some side effects are rare (agranulocytosis, myocarditis), others are common and at least modifiable, if not treatable (constipation, sialorrhoea, drowsiness). Ensuring that prescribers are confident in managing side effects is clearly essential, but it is also important that all staff members involved in patient care are also well-informed. Distressing symptoms may not be recognised as side effects by patients, but care co-ordinators, nurses, occupational therapists, social workers and others may have more regular contact with patients than their psychiatrists do, and these allied healthcare professionals could play a key role in identifying mediation-related problems before they result in patients abandoning treatments. My survey of practitioners found staff members other than doctors and pharmacists are less familiar with clozapine prescribing guidelines, less assured of the effectiveness of clozapine compared with other antipsychotics, and less likely to think that patients under their care required it. Training should therefore target all health professionals, not just prescribers.

It is clear that there is also a need to increase patient awareness of the benefits of clozapine. I found that almost half of patients who would be considered eligible for clozapine treatment had never heard of it (46%), let alone knew anything about it. Clinicians should therefore be mindful not to assume that patients have prior knowledge of clozapine (either in terms of benefits or drawbacks). Rettenbacher et al. (238) found that patients with schizophrenia usually estimated other chronic diseases to be considerably worse than theirs, and so the authors suggested that patients might not take their illness seriously enough to consider taking medication to treat it. Regular discussions between healthcare professionals and patients about schizophrenia and its treatment course may improve this attitude, potentially increasing familiarity with clozapine and decreasing what might be considered a detrimental 'fear of the unknown'. It may also be beneficial to move away from the practice of introducing the idea of an entirely new medication with unique monitoring requirements and side effects at the point of acute psychotic relapse. Instead, the treatment pathway for schizophrenia should be made transparent and clear to patients from the outset of illness. This may make initiating clozapine at a time of severe illness somewhat easier.

Increasing familiarity with clozapine may also help reduce the understandable fear of side effects shown in my survey of patients. Knowing what to expect may improve tolerability, or at least reassure patients that some things are likely to improve with time (drowsiness, dizziness), which might reduce the risk of treatment refusal during the initial stages (when side effects are also likely to be most burdensome). Clozapine support groups could be useful, allowing open discussions with knowledgeable staff members about individual benefits and problems (239). Patient-to-patient support may be of particular value. This idea is largely unexplored in this context, but more commonly employed in physical health conditions. A frequent (and reasonable) complaint expressed by patients during medication counselling is the lack of 'lived' experience of the staff member – they have never taken the drug in question, or experienced the side effects – and this was also commented on by patients in my survey. Patient advocates for clozapine might be perceived as more trustworthy in this regard. Patients with psychotic disorders may be particularly isolated compared to others in terms of access to support groups, as they are less likely to use the

internet or social media. One study showed 56% of patients with schizophrenia use text messaging, 48% have an email address, and just 27% access social media (mostly Facebook) daily (240). In contrast, a survey of patients with asthma found 82% use text messaging, 77% use email, and 65% use Facebook at least weekly (241). Efforts to engage patients early in their treatment pathways, and specifically with respect to clozapine, may help to reduce outright refusal of clozapine initiation, and later discontinuation. Peer support groups should be considered for improvement in medication acceptability, and are of benefit in multiple domains – one Dutch RCT of peer support groups for psychosis demonstrated improvements in social support, self-esteem and quality of life (242).

I have shown so far that a delay to clozapine initiation at this Trust in South East London remains, and have examined the opinions of both clinicians and patients to investigate the possible reasons for this. Next, I considered the possible consequences of this treatment delay on clinical response, using inpatient admissions as the primary outcome. I hypothesised that a longer delay to commencing clozapine may be associated with a less favourable clinical outcome, based on observations in first episode psychosis where longer durations of untreated psychosis are associated with poorer eventual response to treatment (167). I also investigated the effect of continuing or stopping clozapine treatment on long term outcomes.

This study may be considered a 'mirror image' study, with one side of the 'mirror' (pre-clozapine) being compared with the other side (post-clozapine). Several methodological issues in relation to this warrant discussion; the length of time included in the study on each side of the 'mirror', and the point at which the mirror is placed with respect to the inpatient admission during which clozapine was started. Mirror image methods allow for comparisons within patients, which avoids the selection bias that is inherent to the non-randomised nature of observational data. There are, however, drawbacks to this sort of analysis. Symptoms (and therefore requirement for inpatient admission) may naturally subside over time, and the lack of a control group (patients are effectively used as their own 'control') means that this effect may be overlooked. Also due to the non-random sample selection, regression to the

mean is also possible. Finally, asymmetrical treatment durations on each side of the mirror point may also contribute to data bias – generally, the 'post-mirror' period needs to be as long as possible in order to capture a maximum amount of data where it is not known how long the effect of an intervention might last. This is especially true of a disorder such as schizophrenia, where the chronic, relapsing and remitting nature of the illness means that the longer the time period studied, the more translatable the data becomes to a wider population.

There are several options for the length of time included on each side of the mirror point. The first is a straight comparison mirror image, where the length of time included on each side of the mirror point is the total length of the patient journey, from the date of first contact with psychiatric services to the study end point. This is likely to mean that the pre-clozapine period included in the study is a different length to the post-clozapine period and so no within-patient direct comparisons can be made of the data. This method has the advantage of including all available data for each patient, and avoiding any loss of data at the extreme ends of patient journeys. A fixed period mirror image can be used, where the length of time studied is fixed for all participants on either side of the mirror point, e.g. 5 years either side of the mirror point are included. This means that there is no asymmetry in the data as seen with the first method, and it also allows a direct comparison of data between patients as well as within patients, rather than further manipulating the data to provide admission days per time period. However, In order for all patients to be included and be studied for the same time period, this time period has to be set at the shortest pre- or post-clozapine time period within the data set. For this data set, this is just 45 days, and so this method would result in a total study period length of only 90 days, and a large amount of lost data. An individualised mirror image method keeps the time periods on either side of the mirror point equal for each patient, but allows them to be different between patients. The length of the mirrored time period for each patient is the time from first contact with psychiatric services to the clozapine start date (mirror point), or from the mirror point to the end of the study, whichever is longer. The advantage of this technique is the symmetrical studies within each patient, allowing

direct comparison within patients, but maintaining the maximum length of the study period. Nonetheless, some data may be lost at the extreme ends of patient journeys.

The length of the 'mirror' period chosen by other authors varies considerably, but is generally in the range of 1 – 3 years pre- and post-medication initiation. Some authors acknowledge that longer periods of follow up are preferable in order to observe differences in outcomes (84), and longer treatment episodes are likely to reduce regression to the mean, since if the new treatment (clozapine) is started as an inpatient (a time of admission 'cost'), this 'cost' will subside over time (243). This regression to the mean is further neutralised if individualised treatment episodes are considered, i.e. using an individual study period length for each patient (243). The use of a control group can further reduce the risk of regression to the mean, and some studies do use this method (89, 181). However, this introduces a risk of selection bias, which is avoided by including the entire population over a period of time who were 'selected' to start clozapine. Many mirror image studies employ asymmetrical study periods. Commonly, a longer post-mirror (89, 172, 178, 181) period is used, but longer pre-mirror (179, 244) periods are also employed. Asymmetry in the time period studied is a problem if the new treatment takes some time to take effect – shortening the post-mirror period may result in benefits to the new treatment being missed. This may be the case for clozapine, where up to a year is required for response to be demonstrated (245).

I chose to use an individualised mirror image approach, as this reduces regression to the mean by customising each study period to each patient. I used individualised symmetrical mirror image periods. Using a fixed post-study period would mean either using the shortest post-clozapine time period within the data set (1712 days) or removing patients from the analysis who did not have a sufficiently long period of follow up data available. The average post-clozapine time period available for study was 2497 days (range = 1712 – 3551 days), and so restricting the data to the shortest time period would mean a loss of an average of 785 days of data (range = 0 – 1839 days). Additionally, the pre-clozapine study period would also need to be curtailed for the whole data set to the shortest time period available (45 days), resulting in a loss of an average of 2288 days of data (range = 0 – 8879 days). For this

study, each individualised mirror image period was chosen by observing the pre-clozapine time period (time from diagnosis to clozapine initiation) and the post-clozapine time period (time from clozapine initiation to end of study). Whichever time period was shorter was taken as the mirror image period for data collection on each side of the clozapine initiation date for that patient. For example, if a patient had a time from diagnosis to clozapine initiation of 200 days, and a time from clozapine initiation to the end of the study of 175 days, the total mirror image time period would be 350 days (175 x 2), with a pre- and post-clozapine study time of 175 days, disregarding the first 25 days of the pre-clozapine period.

Further to the length of the mirror image period, the way in which the index admission is treated (for patients who started clozapine as an inpatient, this is the admission during which clozapine was initiated) should also be considered. In order to avoid 'double counting' of this admission, it is necessary to consider how this admission should be designated – whether in the 'pre-clozapine' period or the 'post-clozapine' period. Several options were considered. The entire admission could be counted in the pre-clozapine period, as the original reason for admission is assumed to be a psychiatric relapse, which is assumed to be attributable to the failure of the previous antipsychotic medication. However, should clozapine be insufficiently effective and so the patient be subject to inpatient admission for an extended period of time after it is started, these inpatient admission days, arguably due to the failure of clozapine, would be attributed to the previous antipsychotic medication which the patient was no longer taking. Alternatively, the number of days during the index admission before clozapine was started could be attributed to the pre-clozapine period, and the number of days after clozapine was started could be attributed to the post-clozapine period. This has the advantage of taking into account the fact that clozapine may not be considered for initiation immediately during the admission, and indeed other antipsychotics may be trialled first. If this occurs then this time period should not be attributed to clozapine. However, allocating all admission days after the date of clozapine commencement to clozapine also has some problems. Clozapine usually takes 2 weeks to titrate to an 'average' dose, and indeed often longer than this to establish the patient on a stable, effective dose. During this dose titration period, clozapine may not be at a therapeutic plasma concentration, and so this time period

may be considered unfairly attributed to the drug. Additionally, extra physical health monitoring is required during this titration period, meaning that patients are unlikely to be discharged during this time, and so even if clozapine is effective during this period, the patient will remain in hospital and appear (for the purposes of this study), 'unwell'. A further complication is that the date taken as the 'start date' of clozapine in this study was the date at which the patient was registered with the relevant clozapine monitoring company. Patients can start taking clozapine at any point up to 10 days after this date. Excluding the first 14 days of the post-clozapine period from the analysis would remove some of the confounding from the clozapine titration period, although as described above few patients reach stability exactly 2 weeks after starting the drug. A further strategy would be to include the first 14 days of clozapine treatment in the analysis, but to attribute them to the pre-clozapine, rather than the post-clozapine period. Finally, excluding the index admission entirely from the analysis would remove all the problems with 'carry over' costs from the previous treatment, but may also exclude some vital information from the data.

The index admission is treated in various ways by other authors conducting studies with similar methodology. Many authors do not explicitly state how they designated the index admission, but categorise admissions after the index admission as 'rehospitalisation post-clozapine', implying that the entire index admission was attributed to the pre-clozapine period. Where days of admission rather than total numbers of admissions are considered, the simplest form of analysis is frequently employed, assigning all days pre-clozapine to the non-clozapine antipsychotics, and all days after the clozapine start date to clozapine. Aitchison et al. (244) looked at the cost-effectiveness of clozapine in a mirror image study, examining admission data for the 3 years preceding clozapine and comparing it to the year following. They included the index admission in their analysis, and indeed found that excluding it resulted in very low rates of readmission for patients taking clozapine. The majority of other studies choose to exclude the index admission entirely. Meltzer et al. (84) compared admission data for the 2 years before and after starting clozapine, and argued that the index admission should be excluded from this analysis for several reasons. Firstly, the study was not a 'real-life' project but rather patients were enrolled in the trial and then

underwent a drug-free period in the run up to starting clozapine. Other studies that have introduced an artificial admission period for the purpose of the study, or have artificially prolonged the admission period for the purposes of the study, have chosen to include the index admission but shorten it for the purposes of analysis to account for this – Revicki et al. (89) shortened their index admission length to 14 days for this reason. Similarly, Reid et al. (181) excluded 90 days of the post-clozapine admission period from analysis to account for titration of the drug.

Meltzer also argues, in common with many other authors, that a relapse in mental state prior to clozapine initiation should be attributed to the failure of the non-clozapine antipsychotic. He extends this argument to include patients who relapsed and were non-compliant with their previous medication, again arguing that the non-compliance is a failure of the non-clozapine antipsychotic. The fact that clozapine can be initiated as an outpatient is also cited as a reason to exclude the index admission from analysis, since this then means that clozapine cannot be responsible for the initial reason for admission. Even though in clinical practice it is sometimes the case that initiation of clozapine is the sole reason for admission, often owing to resource restrictions for starting it as an outpatient, arguably this cost of admission should nonetheless not be attributed to the drug itself. This was not the opinion held by Drew et al. (178), who attributed the entire index admission to clozapine if it was clear that this admission was prompted expressly for the purpose of initiating the drug. Further, Meltzer points out that the longer the duration of follow up a study employs (in the case of his 1993 study, 2 years), the less relevant the index admission period becomes in the final analysis as cost savings will still be made regardless of its inclusion in calculations. This assertion is backed up by Hayhurst et al. (90) who performed a similar clozapine cost-effectiveness study to Meltzer et al., again studying costs for two years before and after initiation, and finding that by including the index admission, although cost savings for clozapine were smaller, savings were still made.

Faires et al. (177) looked at costs associated with antipsychotic treatment over the period of a year, and performed a detailed sensitivity analysis of 4 different methods for data analysis.

The methods were: a simple pre/post medication analysis; exclusion of the index admission; exclusion of the first 14 days of the post-medication period; and attribution of the first 14 days of the post-medication period to the pre-medication period. Of these methods, the simplest analysis found no difference between the pre- and post-medication periods, perhaps reinforcing the assumption by Meltzer that longer follow up periods are necessary to observe differences. Small differences were seen with the two more complex analyses, where the first 14 days of the new medication were either excluded entirely or attributed to the first medication, but the biggest differences were observed when the index admission was removed entirely from the analysis. The authors concluded that the costs that are attributable to the first medication do have a directional impact on economic costs, but most of these are acute care costs associated with the index admission.

In their mirror image study of the depot medication paliperidone, Taylor et al. (179) also carried out sensitivity analysis, finding (in common with other authors (246)) that excluding the index admission from analysis revealed larger differences in admission data between the pre- and post-medication periods. They also analysed cases by defining the pre-medication period as admissions before the medication was started, but including the days of the index admission up to the point at which the medicine was commenced, and the post-medication period as all admissions after the discharge date of the index admission, rejecting the post-mirror point days of the index admission from analysis. They argued that this method is the most clinically relevant. I chose 5 different methods of data analysis concerning the treatment of the index admission for this study, outlined in detail in chapter 5.

Finally, using an intent to treat method, where all admissions post-clozapine initiation are attributed to clozapine regardless of whether the patient continued to take the treatment or not, is the method most commonly employed by other authors (30, 84, 89, 90, 170, 172, 175, 176, 180, 181, 244). This method assumes that discontinuing the treatment is a sign of treatment failure, and therefore any subsequent admissions are the result of this failure, and the treatment itself. However, the most common reason for clozapine discontinuation has been shown to be non-compliance with either blood tests or the medication itself (117), both

led by patients rather than clinicians, and it could be argued that this is not a failure *per se* of the medication. Others are of the opinion that non-compliance with a medication constitutes failure (84), since the decision by the patient to stop medication is often driven by a lack of insight (which could be considered a failure of the drug to fully treat the illness) or a lack of tolerability. I analysed the data using an intent to treat method, and then separately for those that continued clozapine for the length of the study, and those that discontinued treatment.

Analysis of the intent to treat population found a reduction in the mean number of days of admission per year and in the mean number of admissions per year once clozapine had been started. The reduction in the number of days of admission was statistically significant only where either the entire index admission was discounted, the 2 week period after clozapine initiation was discounted, or the remainder of the index admission after clozapine was started was discounted. The biggest reduction was seen when the latter analysis method was employed. The same pattern of reduction in both mean days of admission per year and mean total admissions per year was also seen for those who continued to take clozapine for the entire length of the study, although here the differences were larger and all analysis methods returned statistically significant results. No significant difference was seen in days of admission per year for those that discontinued clozapine, although a reduction in the total number of admissions per year remained. This sensitivity analysis suggests that the portion of the index admission after clozapine has commenced is highly relevant when considering the overall apparent effectiveness of the drug. The effect of excluding it either entirely or in part is marked, suggesting that it is proportionally lengthy in comparison to any admissions that occur later, after clozapine has been started and after the initial index admission. The finding that those who discontinue clozapine still have a reduction in the total number of admissions per year after the index admission, but no reduction in the mean number of days of admission per year (although not statistically significant, for some methods of data analysis patients who discontinued clozapine had a trend for more days of admission per year after the clozapine had been started) suggests that on average, these patients have longer inpatient admissions than their counterparts who continued to take the clozapine. Presumably this is because admissions are necessary for those that continue clozapine

largely due to temporary treatment breaks, which are quickly remedied with rapid positive results, but for those that discontinue clozapine symptoms remain poorly treated by non-clozapine antipsychotics, necessitating longer inpatient stays. Further research in this topic is required, with detailed examination of the reasons for admission for both patient groups, and for those that discontinued clozapine, in relation to the time at which they stopped the medication.

Overall, I found (in common with previous authors) that clozapine reduced the number of bed days per year (a reduction of 16 – 47 bed days per year for the intent to treat population, depending on the data analysis method) and also the number of inpatient admissions per year (0.7 fewer admissions per patient, per year). These reductions were largely due to the results for those who continued to take the clozapine, with no significant reduction in bed days for those that discontinued during the study. Patients who continued to take clozapine experienced a larger reduction in the mean number of admissions per year (0.8 – 1.5 per patient, per year) compared to those who discontinued the clozapine (0.25 – 0.7 per patient, per year). This finding has significant implications for the economic benefits of clozapine, as well as the obvious benefits for patients in improvement in clinical symptoms. A similar reduction in hospitalisation rates was shown by Ucok and colleagues (100), who demonstrated a drop from 0.87 admissions in the year preceding clozapine initiation to 0.11 in the year following clozapine starting (0.76 fewer admissions per year). In their follow up study, Hayhurst et al. (90) found a comparable reduction in readmissions after clozapine initiation of two thirds, and a drop in bed days of 33 over the two year study. Similarly, Ahn et al. (247) demonstrated a reduction of 22.39 bed days per year in their study of patients in South Korea, and a reduction of 1.45 admissions per year. Larger benefits were reported by Nielsen and colleagues (204) in their two year mirror image study of patients starting clozapine. They found a reduction of 206 bed days in the two year post-clozapine period (103 days per patient per year), and a drop in admissions of 1.5 in the same time period (0.75 admissions per patient per year). Smaller benefits were shown by Latimer et al. (57) of a reduction of 3.4 bed days per year after clozapine initiation. A recent meta-analysis of trials looking at the effect of clozapine on hospital admissions found a median reduction of 34 days

after clozapine initiation (229). Some of the differences in results between studies may be explained by differing patient populations (specifically in terms of illness severity at the time of clozapine initiation, but also demographics), but choice of data analysis method may also have a significant effect, as discussed above. The studies of Ucok, Hayhurst and Nielsen all used mirror image designs similar to that reported in this thesis, with Hayhurst and Nielsen also excluding the index admission from outcome calculations. These latter authors also accounted for patients who discontinued clozapine, in contrast to Ucok, Latimer and Ahn – these authors treated the entire patient cohort as an intent to treat group, with no separate analysis for clozapine continuers or discontinuers. The study conducted by Latimer et al. is somewhat different from the others, gathering data on clozapine use from prescription fills only, and being based only on patients taking clozapine for at least six months. The lack of inclusion of discontinuation of clozapine as a confounding factor may have contributed to their finding of a lower overall benefit of clozapine. Further differences between studies may be explained by variation in inpatient admission criteria between countries and time points.

My study found the length of clozapine delay had no effect on the number of inpatient admissions, or days spent as an inpatient per year, once clozapine had been commenced. This has important implications for prescribers, who can be reassured that clozapine is expected to bring a clinical benefit to their patients irrespective of the length of time they may have spent during their illness taking other antipsychotics. Clozapine should not be withheld from patients even if they have been in contact with mental health services for extended periods of time. Other studies using the same methodology for clinical outcome as that presented in this thesis have also found no statistically significant association between the delay to clozapine use and the number of inpatient admissions after clozapine was started. However, in Harrison et al.'s retrospective review of 402 patients receiving clozapine in New Zealand (99), a shorter delay to clozapine use was associated with fewer previous inpatient hospitalisations, but this correlation failed to reach statistical significance. Of note, only patients who had been taking clozapine for 3 years or more were included in this aspect of their analysis, and the low patient numbers may have underpowered the study. I did not undertake a power calculation for my group, and it is possible that larger patient numbers

would have revealed an association. In contrast, a recent analysis by Ucok et al. (100) used clinician, patient and carer's opinions to assign patients to those with 'good' response and 'minimal or no' response to clozapine. Using these criteria, they found that a 'good' response was associated with a shorter delay to clozapine initiation, when compared to with those in the 'minimal or no' response group. This result may reflect some degree of selection bias, as they also found that 'good' responders were more likely to have had fewer admissions prior to clozapine commencement, suggesting perhaps that these patients suffered a less severe illness course than their counterparts in the 'minimal or no' response group. In Japan, Yoshimura and colleagues reviewed 90 patients with treatment-resistant schizophrenia, all of whom had been taking clozapine for at least 3 months (101). They showed delay to clozapine initiation was a predictor of response to treatment, measured by clinical rating scales. In their study, a 'critical treatment window' of 2.8 years, from time of treatment-resistant diagnosis to clozapine prescription, conferred an 82% response rate if the delay length fell below this cut off, and a 31% response rate and increased likelihood of receiving ECT (electro-convulsive therapy) if above it. Comparing results across these studies is clearly hampered by differing patient populations and data collection and analysis methods.

My study showed an attenuation of the benefits to days spent as an inpatient as the age at which clozapine was introduced increased. This is not simply an effect of older patients having less follow up time in the study, as each patient acted as their own control in my individualised mirror image study. It is also not confounded by the length of delay to clozapine initiation (older patients may have been ill at a time before clozapine was available in the UK) – this factor was found to have no effect on outcomes. This result was found on some statistical measures and not others, so further research is required to establish the strength of this association. Other authors have demonstrated a younger age at onset of schizophrenia and longer durations of illness is associated with poorer response to clozapine (248). The implication of this finding is that those patients who present with symptoms at a younger age have a more severe illness, and that longer treatment durations are related to a progressive and worsening illness course that becomes less responsive to treatment over time. I did not control for age of onset of schizophrenia. It is possible that the patients in the

older age categories also developed schizophrenia at a younger age than those in the younger age cohorts, although this would imply that they had also had longer illness durations and most likely longer clozapine delays, which I did not find to be associated with the outcome variable. A higher illness severity, or increased treatment-resistance at older ages is a plausible explanation, aligning with observations of worsening outcomes with longer durations of untreated psychosis in first-episode schizophrenia (167). Ucok et al. (100) also found that younger patients were more likely to have a 'good' response to clozapine. It is possible that older patients are more likely to have experienced more relapses during their illness course, and more relapses have previously been shown to have an adverse effect on long term outcome (249). Conversely, younger age has also been associated with an increased likelihood of relapse (249) (although other authors have also found no association between response to treatment and age (250)). Whatever the underlying reasons, although my study shows that benefits are found from commencing clozapine at any stage in the treatment course, regardless of age, it also shows an increased benefit from earlier initiation.

My finding of increased long term outcome benefits with initiation of clozapine at a younger age, and the findings of others that shorter delays to clozapine use may result in better treatment-response, prompts questioning of whether clozapine should be initiated even earlier in treatment pathways than currently recommended. The most obvious barrier to use of clozapine as a first line treatment for schizophrenia is the burden of side effects (some, but not all unique to clozapine compared to other antipsychotics) and regular blood tests (unique to clozapine). This might be expected to affect patient acceptability and long term concordance with treatment; indeed, in Woerner et al.'s 2003 trial treating 34 patients with clozapine as a first-line antipsychotic, only 32% remained on clozapine by the end of the year-long study (251), despite response rates of 66%. This response rate demonstrates that clozapine is not only effective in treatment-resistant schizophrenia, but also in non-treatment-resistant illness. This potential was realised by Meltzer and colleagues in a 2 year randomised trial comparing clozapine to typical antipsychotics in non-treatment-resistant schizophrenia (252) – here, clozapine not only provided effective symptom relief, but also reduced relapse and rehospitalisation rates in comparison to the other treatments. A larger,

year-long study conducted by Lieberman et al. (253) also found clozapine superior to a typical antipsychotic (chlorpromazine) in speed of treatment response and time spent in remission for treatment-naïve patients (although there was no difference in overall response, in terms of symptomatology, side effects and overall remission rates).

Although clozapine is effective in both treatment-resistant and non-treatment-resistant schizophrenia, prescribing in treatment-naïve patients remains an unusual practice, and understandably so. Assuming that approximately 30% of patients will either already have, or go on to develop a treatment-resistant illness, this would leave around two thirds of first-episode patients being given clozapine where another antipsychotic would also be effective – arguably subjecting them to unnecessary blood tests and avoidable side effects. Trialling a non-clozapine antipsychotic in the first instance therefore seems reasonable, but if this fails research has shown disappointing efficacy for any antipsychotic other than clozapine. Agid and colleagues applied a treatment algorithm to 123 patients with schizophrenia in Toronto (141), allowing treatment with an atypical antipsychotic initially, followed by a second atypical if this was ineffective, followed by clozapine. Importantly, they dictated a shorter than usual 4 week period to assess treatment response at each stage, so access to clozapine was theoretically possible within the first 8 weeks of presenting to psychiatric services. They found, in common with established evidence, that three quarters of patients responded to the first antipsychotic prescribed. The remaining 25% were given a second atypical medication, and of these just 23% responded (representing only 6% of the entire cohort). The non-responders were offered clozapine, and this had a beneficial effect for 77% of these patients on positive and negative symptoms, as well as overall clinical impressions. Other studies have also demonstrated longer term outcome benefits – Tiihonen et al. describe an observational study of 2230 patients in Finland presenting to inpatient services for the first time (254) and showed that those who received clozapine during this first contact had lower treatment discontinuation rates and rehospitalisation risks compared to those given a variety of other medications, including depots. Overall, patients receiving clozapine (or perphenazine depot or olanzapine) in the first 30 days of hospitalisation had the lowest risk of stopping treatment for any reason, compared to those started on other antipsychotics (or

no antipsychotic). The lowest risk of rehospitalisation in this study was associated with starting perphenazine depot (59% reduction in relative risk compared to haloperidol), followed by olanzapine (41% reduction in relative risk) and clozapine (39% reduction in relative risk). More recently, and with longer follow-up times of up to 20 years, Taipale and colleagues showed that clozapine (and depot antipsychotics) was associated with the lowest risk of rehospitalisation in both chronic and first-episode patients with schizophrenia (255). These studies support an argument for early use of clozapine in the treatment journey.

My study, whilst of a smaller population than those published previously, benefits from wider inclusion criteria and longer follow up times. I did not exclude patients who were in the first few months of treatment, who were acutely unwell, were current inpatients, had received clozapine for less than a defined period of time, or were taking less than a defined number of milligrams of clozapine per day, as other studies have done (99, 100, 204). I have shown that taking clozapine results in a reduction in the number of days spent as an inpatient per year. Patients experience this reduction in bed days regardless of the chronicity of their illness. Clinicians can be confident that prescribing clozapine will confer a positive outcome to their patients regardless of when in the illness course it is started, and they should continue to make every effort to help their patients comply with treatment to maintain this benefit. Further, although I have shown no effect of delay to clozapine initiation on long term outcomes, I have shown that the benefits to clozapine administration may be attenuated with advancing age, suggesting that early initiation of clozapine in the illness is to be recommended. However, my research also shows that this positive effect is maintained only if the patient continues to take the clozapine – if the treatment is stopped, then the number of days spent as an inpatient returns to the level it was before the clozapine was started, in most analyses of the data (in one analysis method more days were spent as an inpatient once clozapine had been stopped, in one other the number of inpatient days was fewer). Other authors have also demonstrated worsening outcomes on stopping clozapine – in Atkinson's case series review of 35 patients who had discontinued clozapine (106), global functioning scores were significantly lower after stopping the drug. Studies using hospitalisation as an outcome measure have similarly reported more readmissions and

increased lengths of stay for patients who discontinue clozapine (90), or surprisingly, no effect on hospitalisation status whether clozapine was continued or not (109). This heterogeneity of results may be due to analysis methods chosen, as I have shown in this thesis, but also local differences in optimisation of clozapine prescribing and side effect management, inpatient admission policies, community support, and other factors that might influence readmissions. Significantly, my separate analysis of data for patients who continued or discontinued clozapine demonstrates the importance of this approach. Analysing patient cohorts on an intent-to-treat basis underrepresents the benefits of clozapine.

Continuing to take clozapine conferred a larger long term benefit to time spent as an inpatient than starting but then stopping the drug. In my final study, described in chapter 6, I found an encouraging two thirds of patients remaining compliant with clozapine during long term follow up. In my cohort, 36% of patients discontinued clozapine at least once. This is not dissimilar to reports by other authors, although reported rates of discontinuation range widely from 16 – 66% (90, 102, 107, 115, 172, 178, 245, 256-258). The same authors also found that the majority of patients who discontinued clozapine did so within the first year of treatment; I did not find this to be the case, with 25% of discontinuers in my study stopping clozapine within the first 229 days (7.5 months).

I used a strict definition of discontinuation (complete and deliberate switch to a different antipsychotic, rather than including brief breaks that resulted in immediate retitration) partly because the non-clozapine antipsychotic prescriptions used to cover brief retitration breaks would not meet the criteria of being ‘adequate treatment episodes’, but also because inconsistent documentation of these episodes made data collection difficult. Most other authors do not define their criteria for discontinuation (115-117, 172). In their 15 year retrospective study of 320 patients taking clozapine, Davis et al. (102) defined any clozapine interruption of more than 4 days as a discontinuation event. In their cohort 57% of patients stopped clozapine at least once, with the highest frequency in the first 3 – 6 months, and just 16% of clozapine discontinuers restarted. Half of the patients in their study had discontinued

clozapine by 6.9 years. In contrast, Munro and colleagues (103) used a discontinuation definition essentially mirroring that described in this thesis – i.e., withdrawal from the central clozapine monitoring service – and found discontinuation rates of 34% in year one, dropping significantly after this. Similarly, Legge et al. (105) defined discontinuation as an absence of a clozapine prescription for at least 3 months, and found a similar clozapine discontinuation rate of 38% in year one.

In my study, of the patients who discontinued clozapine in the study described in this thesis, 71% stopped just once. Of these, 71% restarted treatment with clozapine. To my knowledge, no other research has examined the prescribing patterns on stopping and restarting clozapine or other medications in this degree of detail. The high proportion of patients restarting clozapine is encouraging, suggesting some acknowledged benefit to the treatment in the first instance (or recognition of the lack of benefit of other available options). The majority of medicines chosen for patients who discontinued clozapine the first time were atypical antipsychotics, and this probably reflects local prescribing practices. Interestingly, most patients were switched to oral antipsychotics rather than injectable options, suggesting that non-compliance with oral medication was not the overriding reason for clozapine discontinuation. Few other authors have studied post-clozapine medication choices, and where they have, the local guidelines would be expected to influence choices. A similar study in 2007 in the same Trust found that 44% of patients were switched to a polypharmacy regimen after clozapine was stopped (106). I found just one patient was prescribed polypharmacy in my study, and this may suggest a shift in prescribing practices since the introduction of prescribing improvement programmes (259).

My study demonstrates that it is not possible to predict future clozapine discontinuation from a presenting patient's age, ethnic background, diagnosis or previous treatment history, and this reflects my experience in clinical practice. Previous studies have found that older patients (56, 102-104, 109) and those of African-Caribbean origin (77, 102, 103, 105, 111, 118) are more likely to discontinue clozapine. This variability in reported risks for discontinuation (some authors, in addition to the present study have found no association

between age (111, 112, 118) or ethnicity (111, 112) and stopping clozapine) may be due to population heterogeneity between studies or differing selection criteria for initiating clozapine. Even within similar populations in the same country (subject to the same prescribing guidelines and restrictions), differences have been noted in discontinuation rates within NHS Trusts (104), suggesting that localised clinical practices may also have a significant influence. Growing familiarity with clozapine over the past 25 years will also have played a part.

The data presented here suggest that men are more likely than women to stop clozapine. To my knowledge, male gender has not previously been linked with a higher risk of clozapine discontinuation. This finding is in contrast to results from other authors, including Davis et al. (102) who found in their cohort of 320 patients that females were more likely to stop treatment, although 91% of their cohort were male, and this result lacked statistical significance. In Nielsen et al.'s (204) study of 633 patients, females had a shorter time to readmission to an inpatient unit. It has been suggested previously that male gender is associated with a better response to clozapine (260, 261) and non-response to medication is associated with treatment discontinuation (118). It is possible that in my study, prescribing of clozapine was reserved for more severely ill women than men, resulting in a female cohort with a greater illness burden at baseline who may be less likely to benefit from clozapine – and this has been demonstrated previously (204, 262). However, delay to clozapine initiation and the number of previous antipsychotics prescribed did not differ in my study between men and women, suggesting a similar baseline illness severity, and I did not find women more likely to discontinue clozapine. Conversely, other authors have shown females to respond better to clozapine than males – in Kohler-Forsberg et al.'s Danish study of clozapine patients over two years, women had a greater functional response to clozapine (250), potentially implying a lower likelihood of discontinuation and supporting my findings. The same group also found a shorter time from diagnosis of schizophrenia to clozapine use (although no 'theoretical delay' to prescribing was calculated) conferred an improved response to clozapine, but only in female patients. I did not find delay to clozapine use affected long term outcomes in my cohort.

I have demonstrated that the benefits of clozapine therapy, in terms of reduction in inpatient admissions, are sustained only if patients continue to comply with treatment (187). On clozapine discontinuation, the beneficial reduction in inpatient bed days is lost. Patient non-compliance with therapy and the emergence of adverse effects are consistently noted in the literature as the main reasons for clozapine discontinuation (102, 107, 113, 115-117, 172, 178). In my study, the most common reason for discontinuation of clozapine (when documented) was that the patient refused to continue therapy, rather than it being a prescriber decision based on adverse effects; and this continued to be the case for subsequent clozapine treatment breaks. Whilst it may be considered reassuring that medical crises or blood dyscrasias were not a dominant feature of clozapine discontinuation, the reasons behind patients refusing treatment were not well documented and forms a vital topic for future research. Where possible in this study I elucidated the reason behind patient-driven treatment discontinuation, but found this to be generally poorly recorded in the clinical notes. Where documentation did exist, it was patient refusal of continuing blood tests that dominated reasons for stopping, and I have shown previously that this is a concern raised by clinicians when considering initiating clozapine (263). The risk of clozapine-induced blood dyscrasia decreases exponentially over time (264), and other authors have argued that reducing or stopping the requirement for regular blood monitoring would be justifiable (264). I have suggested that antipathy to blood monitoring may be a recurring reason for treatment cessation by patients, so removing regular blood tests may increase compliance. Alternative strategies aimed at making blood testing simpler or at least more accessible, such as introducing point-of-care testing may also be useful (265).

In conclusion, this study suggests that clozapine discontinuation cannot be predicted from a patient's age, ethnicity, diagnosis, or chronicity of illness. Male patients may be more likely to stop clozapine, but this result requires further investigation. The main reason for discontinuation is reported to be patient refusal to continue with treatment. Despite this, 70% of patients who stopped clozapine were restarted, and of these about two thirds continued to take the medication. Further research should focus on the reasons for patient-led discontinuation of clozapine, with a view to identifying modifiable factors. During this part of

the study five patients died, three of whom were taking clozapine at the time of death. It was beyond the scope of this investigation to pursue the role or otherwise of clozapine in the cause of death, although the frequency with which death was the cause of clozapine discontinuation was lower in my study (8%) than reported elsewhere (13%) (117).

7.1 Limitations

Excepting the practitioner and patient survey aspects to this thesis, the research presented here was conducted using retrospective data collection. The data retrieved by this method are inevitably limited by the quality of clinical data recording. Where available I consulted multiple data sources to gather and verify information, but due to the long follow-up duration of my studies (which add to their strengths) at times this information was inaccessible.

There are several factors which need to be considered with respect to the design of my study into the effects of clozapine on inpatient admissions described in chapter 2. The use of inpatient admission data as a proxy marker for the mental state of a patient may be misleading. Patients may be admitted to psychiatric units for a range of reasons that may not reflect a relapse in mental state, including social reasons. In clinical practice however I feel this is rare, and in the study population in South East London the illness severity required for inpatient admission, given the continued pressure on inpatient bed resources, is generally considered to be high. For these reasons I think it unlikely that patients in my cohort were admitted for reasons other than a relapse in mental illness. I also believe that inpatient bed days are an important outcome in their own right, given the impact of inpatient admissions on scarce health system resources.

Conversely, it is possible that patients were not admitted despite a psychiatric relapse. I did not include input from community-based home treatment or crisis teams, and it is possible that as a result, inpatient admission data were underestimated. However, it is expected that whilst to some degree access to inpatient services may have changed over the course of the study, in general the severity of illness that would prompt inpatient admission is likely to have remained broadly the same, and so this possible source of underestimation of illness should

have remained the same for every patient during the course of the study. It is also true of course that being in (or out) of hospital is not necessarily directly related to increased (or decreased) morbidity.

Further, it is possible that the length of inpatient admissions may have been affected by other factors outside mental state. Wolff et al. (266) found an affective disorder diagnosis and higher disease severity to be associated with longer lengths of stay. Conversely, risk to others, substance abuse, ongoing somatic care needs and male gender were associated with shorter lengths of stay. I did not account for the possible confounders of comorbid affective or physical illness, disease severity, substance abuse or risk of violence. The 'mirror image' nature of this study, using each patient as their own comparator, is expected to minimise the impact of some of this on the overall results since for each individual, social and other factors are likely to remain broadly the same over the study period. However, the mirror-image design also introduces a degree of bias to the results, as it inherently involves non-random assignment of patients, and there is no blinding (including in results evaluation). There are also difficulties making assessments of data based on retrospective clinical note review – I have attempted to overcome these by interrogating multiple data sources where available, including clinic letters and pharmacy dispensing systems. As noted above in relation to the study conducted by Ucok et al. (100), it is possible that patients who were started on clozapine earlier were selected to do so by clinicians because they were thought more likely to respond, or more likely to comply with treatment. It is therefore possible that patients that started clozapine earlier are systematically different to those who started later.

I did not include data on where clozapine was initiated. It is possible that patients who have clozapine initiated in hospital rather than in a community setting are more likely to remain compliant with therapy, as they presumably receive more support and encouragement as the clinical response to clozapine develops. By the same reasoning, patients with longer hospital admissions after stabilising on clozapine treatment may be more likely to continue to comply with treatment if clinical response and insight continues to develop over time. If this is the case, patients under the care of forensic services might be expected to have better

compliance rates with clozapine than other patients, as admission lengths are frequently much longer. I am not aware of data to support this theory but this should be the subject of further study.

A further unfortunate limitation of my research is the lack of detail concerning the reasons for patient refusal to continue with clozapine therapy. This reflects a lack of documentation by clinicians at the time, but may contribute to an underestimation of the influence of adverse effects on decisions to discontinue treatment. My finding that only 7.5% of patients discontinued clozapine due to side effects, a lower proportion than that reported in other studies, either suggests effective management of these by local prescribers or that a proportion of the 'patient refusal' category is in fact, at least in part, because of side effect burden.

The clinician questionnaire study described in chapter 3 was also subject to some methodological problems. The questionnaire was made available to all practitioners at SLaM, but the majority of responses were from younger, trainee psychiatrists. It is likely that this cohort have less influence on treatment plans than their consultant colleagues, and this might explain the apparent disconnect between the guidelines, with which the prescribers claimed to be familiar, and actual prescribing patterns. Since my study, Tungaraza and Farooq (267) have undertaken a similar survey but canvassing the opinions specifically of consultant psychiatrists. They also found that significant proportions of respondents had few clozapine patients currently under their care, and despite widely declaring good exposure to clozapine use, at least at trainee level, gaps in knowledge that implied a lack of familiarity with the drug were demonstrated. Over 80% of consultants in this survey agreed that clozapine was delayed in use, and the main barriers identified largely mirrored my results – concerns around side effects (specifically metabolic) and refusal of blood tests.

Completion of my questionnaire was voluntary, and it may be that some practitioners declined to participate because they do not use clozapine in their current practice. This may have led to over-reporting of familiarity with the guidelines or the medication. SLaM has many 'national' inpatient beds, some specifically for complex cases of treatment-resistant

psychosis. Its practitioners may therefore see a high proportion of patients with significant medical problems that preclude clozapine use, potentially explaining the relatively high level of concern expressed about this in the survey. Equally, the presence of these services may mean the practitioners sampled will have had more exposure to clozapine use, and so a greater awareness of guidelines than in other areas. The survey asked practitioners for their personal views of clozapine prescribing and so individual bias due to previous experiences cannot be ruled out (and some of these experiences may be unique to SLaM, as mentioned). Whilst this may limit the potential for extrapolation of the results to other practitioners or geographical areas, it can be assumed that the influence of personal past experience on subsequent prescribing patterns is a universal phenomenon (128). As the questionnaire was self-reported it is possible that responder biases have influenced the results. This was minimised by conducting the survey anonymously but cannot be excluded.

With regards to the face-to-face patient interviews described in chapter 4, some specific practical issues arose. For many patients some time was needed before the questionnaire was started in order to build a relationship sufficient to allow questions to be answered. This often required a discussion about current medication and side effects. Patients were more likely to disengage from the interview if language was used that focussed on 'you', i.e. 'if *you* take clozapine, *you* need to have regular blood tests'. This often led to immediate discontinuation of the questionnaire as participants misinterpreted this as news that their medication regimen would be changing to clozapine. This difficulty over patient's ability to grasp a hypothetical concept (imagining they might be taking clozapine) was common. Using language that referred instead to 'other people' rather than 'you' (i.e. 'people that take clozapine have to have regular blood tests') helped to depersonalise the idea and reduced the chance of interview termination. It was apparent that to some extent stigma around clozapine contributed to this, as mentioned in the free-text comments provided by some patients.

Not mentioning the word 'research', and instead calling the survey a 'project' also increased the number of patients willing to engage from the start – this may reflect the high number of

approaches patients receive to participate in research projects at SLaM. Starting conversations with 'I am conducting a research project' was often met with comments about not wanting more scans or blood tests or rating scales to be done. Instead, engaging patients with 'I'm interested in this drug that other people sometimes take and I'd like your opinion' was much more successful. Women were more difficult to engage, often displaying more hostility towards the investigator than male patients did. It was not possible to quantify but I suspected that increased sexual disinhibition in male patients meant they were more likely to be willing to participate in interviews with a female interviewer.

Finally, the high levels of thought disorder or distractibility in many patients meant that a lot of time was required to complete questionnaires, with questions taking many minutes to answer. The Likert scales were generally well understood, and the visual prompts very helpful.

7.2 Ways in which this research could have been performed differently

I did not undertake power calculations for any part of this thesis, and it is possible that as a result, some results did not reach statistical significance owing to low patient numbers. The number of patients included in the retrospective data analysis was as large as possible at the time – patients were excluded from analysis for reasons of missing data alone – but numbers could have been increased by lengthening the time window for inclusion in the study.

I made the questionnaire available to as many staff members as possible, and so it was not possible to calculate sample return proportions in my clinician opinions survey. In hindsight, it may have been more valuable to have limited the scope of survey inclusion, allowing calculation of response rate and strengthening the value and generalisability of my results. I did not use any incentives to increase questionnaire return, but doing so may have helped raise response rates.

The age of patients used throughout this research was their age at the end point of the study. As part of the research question was the influence of age on outcomes, the age used should have been the age of the patient at the point of clozapine initiation. However, patients included in the study were those starting clozapine within a 4 year period, and so the impact of this discrepancy is likely to be minimal since the largest margin by which patient age would change would be 4 years.

I did not account for readmissions that occurred within a short time frame of discharge. Other authors have considered readmissions within 2 weeks of hospital discharge as 'immature discharges' (266) that should be counted as part of the previous admission. This is a reasonable argument and I could have considered this in my data analysis. The current method of analysis, discounting the effect of 'immature discharges', would overestimate the numbers of admissions per year (but the numbers of days of admission would remain unchanged).

7.3 Conclusion

I have shown clozapine is effective and underused. It reduces the amount of time spent as an inpatient, yet prescribing is delayed by an average of 4 years. Clinicians think they know when and how to prescribe clozapine, as dictated by overwhelming peer-reviewed evidence and multiple clinical guidelines, yet polypharmacy, supramaximal antipsychotic doses and numerous sequential non-clozapine antipsychotics are all strategies still used for symptom control instead of clozapine. Staff members cite the main reasons for under prescribing being patient refusal to comply with bloods, or intolerability of side effects. Patients themselves have often never heard of clozapine, and the majority would not rule out clozapine outright due to either compulsory blood tests or side effects, although both these issues are highly relevant to them.

The lack of symptom control and increased time spent in hospital notwithstanding, delaying clozapine prescribing makes no difference to its long-term benefits. It does however provide more benefit if patients keep taking it, with reductions in inpatient admissions lost if clozapine

is stopped. Most patients do remain compliant with clozapine, with men being more likely to stop taking it than women.

Improving prescribing rates of clozapine might be achieved by offering dedicated support in the community in order to initiate clozapine. Reducing blood test requirements, or making testing easier would undoubtedly help, as would familiarising patients with the drug earlier on in their treatment pathways, focussing on reducing fear of side effects and the need to explain complex and perhaps unpleasant short-term processes that may provide longer term gains at a time of acute psychotic relapse. Enabling patients to remain compliant with clozapine once it has been started is vital to reduce the likelihood of inpatient admissions. Men may require particular support.

7.4 Further research

Each facet of the research described in this thesis has inevitably generated further questions. In my study of the delay to initiating clozapine, I showed a high proportion of apparently inadequate trials of antipsychotics. Investigating further the reasons for prescribing of inadequate trials may suggest strategies to avoid this phenomenon and speed access to therapeutic treatment (whether clozapine or otherwise). Detailed statistical analysis of this cohort showed that females had longer delays to clozapine initiation than their male counterparts. This finding requires replication and further investigation. A larger sample size is likely to be required, as well as assessment of illness severity between the genders, as this has been suggested as a possible reason for differing prescribing rates. Other authors have also shown differences in delays in starting clozapine between outpatient and inpatient settings (100). This could be examined *post-hoc* from my data.

My study of the effect of clozapine on inpatient admission status found mixed results in detailed statistical analysis for the effects of age on this outcome. This requires further investigation using larger patient cohorts.

Clearly, ensuring compliance with clozapine treatment as far as possible is beneficial. The reasons for discontinuation are multiple, as reported by other authors, but importantly may change over time and differ between treatment settings. Reasons for discontinuation of clozapine were poorly documented in my study, showing that further retrospective data collection for this outcome is unlikely to be helpful. Prospective follow-up of patients taking clozapine may be more helpful, with the added possibility of gathering patient views on clozapine discontinuation in a timely manner. Further, reasons for not restarting clozapine for those patients who discontinue were not studied in this thesis. This is a further barrier point to continued clozapine therapy which is worthy of investigation, with a view to developing strategies to enable resuming treatment. A small case series (268) in 1999 suggested that clozapine is less effective on restarting – this is an important finding not replicated by a larger study. *Post-hoc* analysis of my data, again using inpatient admissions as a proxy marker for efficacy of treatment could be used to investigate this. An extension of this work is to investigate the reasons for readmission to hospital in patients still taking clozapine. Some of this may be temporary non-compliance, not picked up in my study, or other potentially modifiable reasons.

References

1. Fusar-Poli P, Politi P. Paul Eugen Bleuler and the Birth of Schizophrenia (1908). American Journal of Psychiatry. 2008;165:1407.
2. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 2000.
3. Organization WH. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines: Geneva: World Health Organization; 1992.
4. Singleton N, Bumpstead R, O'Brien M, Lee A, Meltzer H. Psychiatric morbidity among adults living in private households. Office for National Statistics. 2000.
5. Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, et al. Schizophrenia: manifestations, incidence and course in different cultures A World Health Organization Ten-Country Study. Psychological Medicine Monograph Supplement. 1992;Supplement:1-97.
6. Barbato A. Schizophrenia and public health. Division of Mental Health and Prevention of Substance Abuse, World Health Organization. 1998:1-32.
7. Chang C-K, Hayes RD, Perera G, Broadbent MTM, Fernandes AC, Lee WE, et al. Life Expectancy at Birth for People with Serious Mental Illness and Other Major Disorders from a Secondary Mental Health Care Case Register in London. PLoS ONE. 2011;6(5):e19590.
8. Janca A, Kastrup M, Katschnig H, López-Ibor J, Mezzich JE, Sartorius N. The World Health Organization Short Disability Assessment Schedule (WHO DAS-S): a tool for the assessment of difficulties in selected areas of functioning of patients with mental disorders. Social Psychiatry and Psychiatric Epidemiology. 1996;31(6):349-54.
9. NHS Health and Social Care Information Centre. Attitudes to Mental Illness - 2011 Survey Report. 2011.
10. The Schizophrenia Commission. The Abandoned Illness. 2012.
11. McEvoy JP. The Costs of Schizophrenia. J Clin Psych. 2007;68 (suppl 14):4-7.
12. Knapp M, Mangalore R, Simon J. The global costs of schizophrenia. Schizophrenia Bulletin; Schizophrenia Bulletin. 2004;30(2):279.
13. Keefe RS, Mohs RC, Losonczy MF, Davidson M, Silverman JM, Kendler KS, et al. Characteristics of very poor outcome schizophrenia. Am J Psychiatry. 1987;144(7):889-95. Epub 1987/07/01.
14. Keefe RS, Frescka E, Apter SH, Davidson M, Macaluso JM, Hirschowitz J, et al. Clinical characteristics of Kraepelinian schizophrenia: replication and extension of previous findings. Am J Psychiatry. 1996;153(6):806-11. Epub 1996/06/01.
15. Ban TA. Fifty years chlorpromazine: a historical perspective. Neuropsychiatric Disease and Treatment. 2007;3(4):495-500.
16. Stahl SM. Stahl's essential psychopharmacology: neuroscientific basis and practical applications: Cambridge university press; 2013.
17. Joint Formulary Committee. British National Formulary 67. BMJ Group, Pharmaceutical Press,. 2014.
18. Crilly J. The history of clozapine and its emergence in the US market: a review and analysis. History of psychiatry. 2007;18(1):39-60. Epub 2007/06/22.
19. Idänpään-Heikkilä J, Alhava E, Olkinuora M, Palva I. Clozapine and agranulocytosis. The Lancet. 1975;306(7935):611.
20. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic: a double-blind comparision with chlorpromazine. Archives of General Psychiatry. 1988;45(9):789-96.
21. Kane JM, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic - results of a US multicenter trial. Psychopharmacology. 1989;99:S 60-S 3.
22. Claghorn J, Honigfeld G, Abuzzahab FS, Wang R, Steinbook R, Tuason V, et al. The risks and benefits of clozapine versus chlorpromazine. J Clin Psychopharmacol. 1987;7(6):377-84.
23. Honigfeld G. Clozapine: antipsychotic activity in treatment resistant schizophrenics. Advances in Therapy. 1984;1:77 - 97.
24. Kuha S, Miettinen E. Long-term effect of clozapine in schizophrenia a retrospective study of 108 chronic schizophrenics treated with clozapine for up to 7 years. Nordic Journal of Psychiatry. 1986;40(3):225-30.
25. Juul Povlsen U, Noring U, Fog R, Gerlach J. Tolerability and therapeutic effect of clozapine. A retrospective investigation of 216 patients treated with clozapine for up to 12 years. Acta Psychiatr Scand. 1985;71(2):176-85.

26. Lindström LH. The effect of long-term treatment with clozapine in schizophrenia: A retrospective study in 96 patients treated with clozapine for up to 13 years. Acta Psychiatrica Scandinavica. 1988;77(5):524-9.
27. Anderman B, Griffith RW. Clozapine-Induced Agranulocytosis: A Situation Report up to August 1976. European Journal of Clinical Pharmacology. 1977;11:199 - 201.
28. Marder SR, Van Putten T. Who should receive clozapine? Archives of General Psychiatry. 1988;45(9):865-7.
29. Fischer-Cornelssen KA, Ferner UJ. An example of European multicenter trials: Multispectral analysis of clozapine. Psychopharmacol Bull. 1976;12:34-9.
30. Breier A, Buchanan RW, Irish D, Carpenter WT. Clozapine treatment of outpatients with schizophrenia - outcome and long term response patterns. Hospital and Community Psychiatry. 1993;44(12):1145-9
31. Shen WW. A history of antipsychotic drug development. Comprehensive Psychiatry. 1999;40(6):407-14.
32. Cavallaro R, Colombo C, Smeraldi E. A pilot, open study on the treatment of refractory schizophrenia with risperidone and clozapine. Human Psychopharmacology: Clinical and Experimental. 1995;10(3):231-4.
33. Cavallaro R, Brambilla P, Smeraldi E. The sequential treatment approach to resistant schizophrenia with risperidone and clozapine. Human Psychopharmacology. 1998;13(2):91-7.
34. Bondolfi G, Dufour H, Patris M, May JP, Billeter U, Eap CB, et al. Risperidone vs clozapine in treatment resistant schizophrenia - a randomized double blind study. American Journal of Psychiatry. 1998;155(4):499-504.
35. Lindenmayer J-P, Iskander A, Park M, Apergi F-S, Czobor P, Smith R, et al. Clinical and neurocognitive effects of clozapine and risperidone in treatment refractory schizophrenics: a prospective study. J Clin Psychiatry. 1998;59:521-7.
36. Flynn SW, MacEwan GW, Altman S, Kopala LC, Fredrikson DH, Smith GN, et al. An open comparison of clozapine and risperidone in treatment-resistant schizophrenia. Pharmacopsychiatry. 1998;31(1):25-9.
37. Sharif ZA, Raza A, Ratakonda SS. Comparative efficacy of risperidone and clozapine in the treatment of patients with refractory schizophrenia or schizoaffective disorder: A retrospective analysis. Journal of Clinical Psychiatry. 2000;61(7):498-504.
38. Tollefson GD, Birkett MA, Kiesler GM, Wood AJ. Double-blind comparison of olanzapine vs clozapine in schizophrenic patients clinically eligible for treatment with clozapine. Biological Psychiatry. 1998;49(1):52-63.
39. Kumra S, Kranzler H, Gerbino-Rosen G, Kester HM, DeThomas C, Kafantaris V, et al. Clozapine and "High-Dose" Olanzapine in Refractory Early-Onset Schizophrenia: A 12-Week Randomized and Double-Blind Comparison. Biological Psychiatry. 2008;63(5):524-9.
40. Littrell KH, Johnson CG, Hilligoss NM, Peabody CD, S.H. L. Switching clozapine responders to olanzapine. Journal of Clinical Psychiatry. 2000;61(12):912-5.
41. Henderson DC, Nasrallah RA, Goff DC. Switching from clozapine to olanzapine in treatment resistant schizophrenia - safety, clinical efficacy and predictors of response. Journal of Clinical Psychiatry. 1998;59(11):585-8.
42. Meltzer HY. Risperidone and clozapine for treatment-resistant schizophrenia. American Journal of Psychiatry. 1999;156(7):1126-7.
43. Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, et al. Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. JAMA psychiatry. 2016;73(3):199-210. Epub 2016/02/05.
44. Taylor DM. Clozapine for Treatment-Resistant Schizophrenia: Still the Gold Standard? CNS Drugs. 2017;31(3):177-80.
45. Conley RR, Buchanan RW. Evaluation of treatment-resistant schizophrenia. Schizophrenia Bulletin. 1997;23(4):663-74.
46. Noel JM. ASHP therapeutic position statement on the use of second-generation antipsychotic medications in the treatment of adults with psychotic disorders. American Journal of Health-System Pharmacy. 2007;64(8):863-76.
47. Moore TS, Buchanan RW, Buckley PF, Chiles JA, Conley RR, Crismon ML, et al. The Texas medication Algorithm project antipsychotic algorithm for schizophrenia: 2006 Update. Journal of Clinical Psychiatry. 2007;68(11):1751--62.
48. National Institute for Health and Clinical Excellence. Schizophrenia. 2010;CG82.
49. Barnes TR. Evidence-based guidelines for the pharmacological treatment of schizophrenia: Recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology. 2011;25(5):567-620.

50. Brenner HD, Dencker SJ, Goldstein MJ, Hubbard JW, Keegan DL, Kruger G, et al. At Issue: Defining Treatment Refractoriness in Schizophrenia. Schizophrenia Bulletin. 1990;16(4):551-61.
51. Gaebel W, Weinmann S, Sartorius N, Rutz W, McIntyre JS. Schizophrenia practice guidelines: international survey and comparison. The British Journal of Psychiatry. 2005;187(3):248-55.
52. Bachmann C, Aagaard L, Bernardo M, Brandt L, Cartabia M, Clavenna A, et al. International trends in clozapine use: a study in 17 countries. Acta Psychiatrica Scandinavica. 2017.
53. Manuel JI, Essock SM, Wu Y, Pangilinan M, Stroup S. Factors associated with initiation on clozapine and on other antipsychotics among Medicaid enrollees. Psychiatr Serv. 2012;63(11):1146-9. Epub 2012/11/03.
54. Stroup TS, Gerhard T, Crystal S, Huang C, Olfson M. Geographic and Clinical Variation in Clozapine Use in the United States. Psychiatr Serv. 2013. Epub 2013/11/16.
55. Juarez-Reyes MG, Shumway M, Battle C, Bacchetti P, Hansen MS, Hargreaves WA. Effects of stringent criteria on eligibility for clozapine among public mental health clients. Psychiatric Services. 1995;46:801-6.
56. Krivoy A, Malka L, Fischel T, Weizman A, Valevski A. Predictors of clozapine discontinuation in patients with schizophrenia. Int Clin Psychopharmacol. 2011;26(6):311-5. Epub 2011/08/19.
57. Latimer E, Wynant W, Clark R, Malla A, Moodie E, Tamblyn R, et al. Underprescribing of clozapine and unexplained variation in use across hospitals and regions in the Canadian province of Quebec. Clin Schizophr Relat Psychoses. 2013;7(1):33-41. Epub 2013/02/01.
58. Koen L MP, Niehaus DJ, Le Roux A. Antipsychotic prescription patterns in Xhosa patients with schizophrenia or schizoaffective disorder. Afr J Psychiatry. 2008;11:287 - 90.
59. Alessi-Severini S, Le Dorze J-A, Nguyen D, Honcharik P, Eleff M. Clozapine Prescribing in a Canadian Outpatient Population. PLoS ONE. 2013;8(12):e83539.
60. Vella S, Pai N. Prevalence & Prescription: Prescribing Practices of Clozapine in Australia between 2005 & 2010. Online Journal of Health and Allied Sciences. 2012;11(1).
61. G. T. Pharmacoepidemiology of psychotropic drugs in patients with severe mental disorders in Italy. Italian Collaborative Study Group on the Outcome of Severe Mental Disorders. Eur J Clin Pharmacol. 1999;55(9):685-90.
62. Verdoux H, Pambrun E, Cortaredona S, Coldefy M, Le Neindre C, Tournier M, et al. Geographical disparities in prescription practices of lithium and clozapine: a community-based study. Acta Psychiatr Scand. 2016;133(6):470-80. Epub 2016/01/31.
63. Nielsen J, Røge R, Schjerning O, Sørensen HJ, Taylor D. Geographical and temporal variations in clozapine prescription for schizophrenia. European Neuropsychopharmacology. 2012;In press.
64. Gaebel W, Riesbeck M, Janssen B, Schneider F, Held T, Mecklenburg H, et al. Atypical and typical neuroleptics in acute schizophrenia and related delusional disorders. Drug choice, switching and outcome under naturalistic treatment conditions. European archives of psychiatry and clinical neuroscience. 2003;253(4):175-84. Epub 2003/08/12.
65. Jönsson EG, Saetre P, Vares M, Strålin P, Levander S, Lindström E. Use of antipsychotics — An analysis of lifetime treatment in 66 patients with psychoses. Psychiatry Research. 2011;187(1–2):80-8.
66. Wheeler AJ. Treatment Pathway and Patterns of Clozapine Prescribing for Schizophrenia in New Zealand. The Annals of pharmacotherapy. 2008;42(6):852-60.
67. Xiang YT, Wang CY, Si TM, Lee EHM, He YL, Ungvari GS, et al. Clozapine use in schizophrenia: Findings of the Research on Asia Psychotropic Prescription (REAP) studies from 2001 to 2009. Australian and New Zealand Journal of Psychiatry. 2011;45(11):968-75.
68. Kinon BJ, Kane JM, Perovich R, Ismi M, Koreen A. Influence of Neuroleptic Dose and Class in Treatment-Resistant Schizophrenia Relapse. Presented at the 32nd Annual Meeting of the New Clinical Drug Evaluation Unit, Key Biscayne, FL,. 1992.
69. Kinon BJ, Kane JM, Johns C, Perovich R. Treatment of neuroleptic-resistant schizophrenic relapse. Psychopharmacology Bulletin. 1993;29(2):309-14.
70. Agid O, Arenovich T, Sajeev G, Zipursky RB, Kapur S, Foussias G, et al. An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. J Clin Psych. 2011;72(11):1439-44.
71. Taylor DM, Young C, Paton C. Prior antipsychotic prescribing in patients currently receiving clozapine: a case note review. J Clin Psychiatry. 2003;64(1):30-4. Epub 2003/02/20.

72. Najim H, Heath D, Singh P. Antipsychotic prescribing before Clozapine in a community psychiatric hospital: a case note review. Psychiatria Danubina. 2013;25 Suppl 2:S165-70.
73. Wheeler A, Feetam C, Harrison J. Pathway to Clozapine Use: A Comparison Between a Patient Cohort from New Zealand and a Cohort from the United Kingdom. Clinical Drug Investigation. 2014;34(3):203-11.
74. Thompson JV, Clark JM, Legge SE, Kadra G, Downs J, Walters JT, et al. Antipsychotic polypharmacy and augmentation strategies prior to clozapine initiation: a historical cohort study of 310 adults with treatment-resistant schizophrenic disorders. Journal of Psychopharmacology. 2016;30(5):436-43.
75. Wheeler A, Humberstone V, Robinson E, Sheridan J, Joyce P. Impact of audit and feedback on antipsychotic prescribing in schizophrenia. Journal of Evaluation in Clinical Practice. 2009;15(3):441-50.
76. Brugnoli R. Novick D. FS, Rossi A., Suarez D., Haro J.M. Efficacy of antipsychotic treatment in schizophrenia: results after 24 months in Italian patients in the Schizophrenia Outpatient Health Outcomes (SOHO) study. Italian Journal of Psychopathology. 2007;13(3):330-40.
77. Kelly DL, Dixon LB, Kreyenbuhl JA, Medoff D, Lehman AF, Love RC, et al. Clozapine utilization and outcomes by race in a public mental health system: 1994-2000. The Journal of clinical psychiatry. 2006;67(9):1404-11. Epub 2006/10/05.
78. Purcell H, Lewis S. Postcode prescribing in psychiatry: Clozapine in an English county. Psychiatric Bulletin. 2000;24(11):420-2.
79. Hayhurst KP, Brown P, Lewis SW. Postcode prescribing for schizophrenia. The British Journal of Psychiatry. 2003;182(4):281-3.
80. Downs J, Zinkler M. Clozapine: national review of postcode prescribing. Psychiatric Bulletin. 2007;31(10):384-7.
81. Tang Y, Horvitz-Lennon M, Gellad WF, Lave JR, Chang C-CH, Normand S-L, et al. Prescribing of Clozapine and Antipsychotic Polypharmacy for Schizophrenia in a Large Medicaid Program. Psychiatric Services. 2017:appi. ps. 201600041.
82. Swinton M, Ahmed AG. Reasons for non-prescription of clozapine in treatment-resistant schizophrenia. Criminal Behaviour and Mental Health. 1999;9(3):207-14.
83. Essock SM, Hargreaves WA, Covell NH, Goethe J. Clozapine's effectiveness for patients in state hospitals: Results from a randomized trial. Psychopharmacology Bulletin. 1996;32(4):683-97.
84. Meltzer HY, Cola P, Way L, Thompson PA, Bastani B, Davies MA, et al. Cost effectiveness of clozapine in neuroleptic-resistant schizophrenia. American Journal of Psychiatry. 1993;150:1630-8.
85. Jonsson D, Walinder J. Cost-effectiveness of clozapine treatment in therapy-refractory schizophrenia. Acta Psychiatrica Scandinavica. 1995;92(3):199-201.
86. Rosenheck R, Cramer J, Allan E, Erdos J, Frisman LK, Xu W, et al. Cost-effectiveness of clozapine in patients with high and low levels of hospital use. Archives of General Psychiatry. 1999;56(6):565-72.
87. Rosenheck R, Cramer J, Xu W, Grabowski J, Douyon R, Thomas J, et al. Multiple outcome assessment in a study of the cost-effectiveness of clozapine in the treatment of refractory schizophrenia. Health Services Research. 1998;33(51):1237-61.
88. Revicki DA. Pharmacoeconomic evaluation of treatments for refractory schizophrenia - clozapine related studies. Journal of Clinical Psychiatry. 1999;60(SUPPL. 1):7-11.
89. Revicki DA, Luce BR, Weschler JM, Brown RE, Adler MA. Cost-effectiveness of clozapine for treatment-resistant schizophrenic patients. Hospital & Community Psychiatry. 1990;41(8):850-4.
90. Hayhurst KP, Brown P, Lewis SW. The cost-effectiveness of clozapine: a controlled, population-based, mirror-image study. Journal of Psychopharmacology. 2002;16(2):169-75.
91. Tang Y.-I. MP-X, Jiang F.,Chen Q.,Wang C.-Y.,Cai Z.-J.,Mitchell P.B. Clozapine in China. Pharmacopsychiatry. 2008;41(1):1-9.
92. Weiss KA, Smith TE, Hull JW, Piper AC, Huppert JD. Predictors of Risk of Nonadherence in Outpatients With Schizophrenia and Other Psychotic Disorders. Schizophrenia Bulletin. 2002;28(2):341-9.
93. Castle D, Castle D, Morgan V, Jablensky A. Antipsychotic Use in Australia: The Patients' Perspective. Australian and New Zealand Journal of Psychiatry. 2002;36(5):633-41.
94. Wolfson PM, Paton C. Clozapine audit: What do patients and relatives think? Journal of Mental Health. 1996;5(3):267-74.

95. Taylor DS, L.; Laverick, G.; Bond, J.;Munro, J. Clozapine: a survey of patient perceptions. Psychiatric Bulletin. 2000;24:450-2.
96. Waserman J, Criollo M. Subjective Experiences of Clozapine Treatment by Patients With Chronic Schizophrenia. Psychiatric Services. 2000;51(5).
97. Angermeyer MC, Loffler W, Muller P, Schulze B, Priebe S. Patients' and relatives' assessment of clozapine treatment. Psychological Medicine. 2001;31(03):509-17.
98. Takeuchi I, Hanya M, Uno J, Amano Y, Fukai K, Fujita K, et al. A Questionnaire-based Study of the Views of Schizophrenia Patients and Psychiatric Healthcare Professionals in Japan about the Side Effects of Clozapine. Clinical Psychopharmacology and Neuroscience. 2016;14(3):286.
99. Harrison J, Janlov M, Wheeler AJ. Patterns of clozapine prescribing in a mental health service in New Zealand. Pharm World Sci. 2010;32(4):503-11. Epub 2010/06/08.
100. Ucok A, Cikrikcili U, Karabulut S, Salaj A, Ozturk M, Tabak O, et al. Delayed initiation of clozapine may be related to poor response in treatment-resistant schizophrenia. Int Clin Psychopharmacol. 2015;30(5):290-5. Epub 2015/07/15.
101. Yoshimura B, Yada Y, So R, Takaki M, Yamada N. The critical treatment window of clozapine in treatment-resistant schizophrenia: Secondary analysis of an observational study. Psychiatry Research. 2017;250:65-70.
102. Davis M, Fuller M, Strauss M, Konicki P, Jaskiw G. Discontinuation of clozapine: a 15-year naturalistic retrospective study of 320 patients. Acta Psychiatrica Scandinavica. 2013.
103. Munro J, O'Sullivan D, Andrews C, Arana A, Mortimer A, Kerwin R. Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. Br J Psychiatry. 1999;175:576-80. Epub 2000/05/02.
104. Whiskey E, Wykes T, Duncan-McConnell D, Haworth E, Walsh N, Hastilow S. Continuation of clozapine treatment: practice makes perfect. Psychiatric Bulletin. 2003;27(6):211-3.
105. Legge SE, Hamshere M, Hayes RD, Downs J, O'Donovan MC, Owen MJ, et al. Reasons for discontinuing clozapine: A cohort study of patients commencing treatment. Schizophr Res. 2016;174(1-3):113-9. Epub 2016/05/24.
106. Atkinson JM, Douglas-Hall P, Fischetti C, Sparshatt A, Taylor DM. Outcome following clozapine discontinuation: a retrospective analysis. J Clin Psychiatry. 2007;68(7):1027-30. Epub 2007/08/10.
107. Ciapparelli A. DOL, Di Poggio A.B.,Carmassi C.,Cecconi D.,Fenzi M.,Chiavacci M.C.,Bottai M.,Ramacciotti C.E.,Cassano G.B. Clozapine in treatment-resistant patients with schizophrenia, schizoaffective disorder or psychotic bipolar disorder - a naturalistic 48 month follow up study. Journal of Clinical Psychiatry. 2003;64(4):451-8.
108. Kelly DL, Kreyenbuhl J, Dixon L, Love RC, Medoff D, Conley RR. Clozapine underutilization and discontinuation in African Americans due to leucopenia. Schizophrenia bulletin. 2007;33(5):1221-4. Epub 2006/12/16.
109. Laker MK, Duffett RS, Cookson JC. Long-term outcome with clozapine: comparison of patients continuing and discontinuing treatment. Int Clin Psychopharmacol. 1998;13(2):75-8. Epub 1998/07/21.
110. Haro JM, Novick D, Belger M, Jones PB. Antipsychotic type and correlates of antipsychotic treatment discontinuation in the outpatient treatment of schizophrenia. Eur Psychiatry. 2006;21(1):41-7. Epub 2006/01/18.
111. Moeller FG, Chen YW, Steinberg JL, Petty F, Ripper GW, Shah N, et al. Risk factors for clozapine discontinuation among 805 patients in the VA hospital system. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists. 1995;7(4):167-73. Epub 1995/12/01.
112. Rascati KL, Rascati EJ. Use of clozapine in Texas state mental health facilities. American journal of hospital pharmacy. 1993;50(8):1663-6. Epub 1993/08/01.
113. Taylor M. SP, Lawrie S.M. Comparing the use and discontinuation of antipsychotics in clinical practice: An observational study. Journal of Clinical Psychiatry. 2008;69(2):240-5.
114. Essock SM, Hargreaves WA, Dohm FA, Goethe J, Carver L, Hipshman L. Clozapine eligibility among state hospital patients. Schizophrenia Bulletin. 1996;22(1):15-25.
115. Pai NB, Vella SC. Reason for clozapine cessation. Acta Psychiatrica Scandinavica. 2012;125(1):39-44.
116. Matza LS, Phillips GA, Revicki DA, Ascher-Svanum H, Malley KG, Palsgrove AC, et al. Validation of a clinician questionnaire to assess reasons for antipsychotic discontinuation and continuation among patients with schizophrenia. Psychiatry Research. 2012;200(2–3):835-42.

117. Taylor DM, Douglas-Hall P, Olofinjana B, Whiskey E, Thomas A. Reasons for discontinuing clozapine: matched, case–control comparison with risperidone long-acting injection2009 2009-02-01 00:00:00. 165-7 p.
118. Rosenheck R, Chang S, Choe Y, Cramer J, Xu W, Thomas J, et al. Medication continuation and compliance: A comparison of patients treated with clozapine and haloperidol. Journal of Clinical Psychiatry. 2000;61(5):382-6.
119. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. New England Journal of Medicine. 2005;353(12):1209-23.
120. Haro J.M. EET, Novick D.,Alonso J.,Kennedy L.,Jones P.B.,Ratcliffe M.,Breier A. Effectiveness of antipsychotic treatment for schizophrenia - 6-Month results of the Pan-European Schizophrenia Outpatient Health Outcomes (SOHO) study. Acta Psychiatrica Scandinavica. 2005;111(3):220-31.
121. Mistry H, Osborn D. Underuse of clozapine in treatment-resistant schizophrenia. Advances in Psychiatric Treatment. 2011;17(4):250-5.
122. Mortimer AM, Singh P, Shepherd CJ, Puthiryackal J. Clozapine for treatment-resistant schizophrenia: National Institute of Clinical Excellence (NICE) guidance in the real world. Clin Schizophr Relat Psychoses. 2010;4(1):49-55. Epub 2010/07/21.
123. Royal College of Psychiatrists. Report of the National Audit of Schizophrenia. Healthcare Quality Improvement Partnership; 2012.
124. Cirulli G. Clozapine prescribing in adolescent psychiatry: survey of prescribing practice in in-patient units. Psychiatric Bulletin. 2005;29(10):377-80.
125. Kissling W. Compliance, quality assurance and standards for relapse prevention in schizophrenia. Acta Psychiatrica Scandinavica. 1994;89:16-24.
126. Patel MX, Nikolaou V, David AS. Psychiatrists' attitudes to maintenance medication for patients with schizophrenia. Psychological Medicine. 2003;33(1):83-9.
127. Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrists' attitude towards and knowledge of clozapine treatment. Journal of Psychopharmacology. 2010;24(7):965-71.
128. Barley M, Pope C, Chilvers R, Sipos A, Harrison G. Guidelines or mindlines? A qualitative study exploring what knowledge informs psychiatrists decisions about antipsychotic prescribing. Journal of Mental Health. 2008;17(1):9-17.
129. Lloyd HM, Markwick AJ, Page ER, Lewis S, Barnes TRE. Attitudes to atypical and conventional antipsychotic drug treatment in clinicians participating in the CUTLASS study. International Journal of Psychiatry in Clinical Practice. 2005;9(1):35-40.
130. Bauer MS. A Review of Quantitative Studies of Adherence to Mental Health Clinical Practice Guidelines. Harvard Review of Psychiatry. 2002;10(3):138-53.
131. Weinmann S, Koesters M, Becker T. Effects of implementation of psychiatric guidelines on provider performance and patient outcome: systematic review. Acta Psychiatrica Scandinavica. 2007;115(6):420-33.
132. Weinmann S, Janssen B, Gaebel W. Guideline adherence in medication management of psychotic disorders: an observational multisite hospital study. Acta Psychiatrica Scandinavica. 2005;112(1):18-25.
133. Hamann J, Mischo C, Langer B, Leucht S, Kissling W. Physicians' and patients' involvement in relapse prevention with antipsychotics in schizophrenia. Psychiatr Serv. 2005;56(11):1448-50. Epub 2005/11/12.
134. Stewart MA. Effective physician-patient communication and health outcomes: a review. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 1995;152(9):1423-33. Epub 1995/05/01.
135. Hodge K, Jespersen S. Side-effects and treatment with clozapine: A comparison between the views of consumers and their clinicians. International Journal of Mental Health Nursing. 2008;17(1):2-8.
136. Day JC, Kinderman P, Bentall R. A comparison of patients' and prescribers' beliefs about neuroleptic side-effects: prevalence, distress and causation. Acta Psychiatrica Scandinavica. 1998;97(1):93-7.
137. Lieberman JA, Kane JM, Johns CA. Clozapine: guidelines for clinical management. The Journal of clinical psychiatry. 1989;50(9):329-38. Epub 1989/09/01.
138. Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines. 10th ed. Abingdon: Taylor and Francis; 2010.
139. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. The American journal of psychiatry. 2011;168(6):603-9. Epub 2011/03/03.

140. NICE. Schizophrenia: core interventions in the treatment and management of schizophrenia in primary and secondary care (clinical guideline 1). London: National Institute for Clinical Excellence; 2002.
141. Agid O, Remington G, Kapur S, Arenovich T, Zipursky RB. Early use of clozapine for poorly responding first-episode psychosis. Journal of Clinical Psychopharmacology. 2007;27(4):369-73.
142. Agid O, Arenovich T, Sajeev G, Zipursky RB, Kapur S, Foussias G, et al. An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. The Journal of clinical psychiatry. Epub 2011/04/05.
143. Taylor D. Psychopharmacology and adverse effects of antipsychotic long-acting injections: a review. The British Journal of Psychiatry. 2009;195(52):S13-S9.
144. Joint Formulary Committee. British National Formulary 61. BMJ group, Pharmaceutical Press. 2011.
145. Paton C, Barnes TRE, Cavanagh M-R, Taylor D, Lelliott P. High-dose and combination antipsychotic prescribing in acute adult wards in the UK: the challenges posed by p.r.n. prescribing. The British Journal of Psychiatry. 2008;192(6):435-9.
146. Field A. Discovering Statistics using IBM SPSS Statistics: Sage Publications Ltd.; 2013. 952 p.
147. Kenny DA. Statistics for the social and behavioral sciences. Boston: Little, Brown; 1987.
148. Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. The British Journal of Psychiatry. 2012;201(6):481-5.
149. Gee S, Vergunst F, Howes O, Taylor D. Practitioner attitudes to clozapine initiation. Acta Psychiatrica Scandinavica. 2013:n/a-n/a.
150. Taylor D, Shapland L, Laverick G, Bond J, Munro J. Clozapine - A survey of patient perceptions. Psychiatric Bulletin. 2000;24(12):450-2.
151. Finlay WML, Lyons E. Methodological Issues in Interviewing and Using Self-Report Questionnaires With People With Mental Retardation. Psychological Assessment. 2001;13(3):319-35.
152. Haas GL, Garratt LS, Sweeney JA. Delay to first antipsychotic medication in schizophrenia: Impact on symptomatology and clinical course of illness. Journal of Psychiatric Research. 1998;32(3-4):151-9.
153. Clarke M, Whitty P, Browne S, McTigue O, Kamali M, Gervin M, et al. Untreated illness and outcome of psychosis. British Journal of Psychiatry. 2006;189(SEP.):235-40.
154. Tirupati NS, Rangaswamy T, Raman P. Duration of untreated psychosis and treatment outcome in schizophrenia patients untreated for many years. Australian and New Zealand Journal of Psychiatry. 2004;38(5):339-43.
155. Alptekin K, Erkoç Ş, Göğüş AK, Kültür S, Mete L, Üçok A, et al. Disability in schizophrenia: Clinical correlates and prediction over 1-year follow-up. Psychiatry Research. 2005;135(2):103-11.
156. Üçok A, Polat A, Çakır S, Genç A. One year outcome in first episode schizophrenia. European archives of psychiatry and clinical neuroscience. 2006;256(1):37-43.
157. Vyas NS, Hadjulis M, Vourdas A, Byrne P, Frangou S. The Maudsley early onset schizophrenia study. Predictors of psychosocial outcome at 4-year follow-up. European child & adolescent psychiatry. 2007;16(7):465-70.
158. Norman RMG, Mallal AK, Manchanda R, Windell D, Harricharan R, Takhar J, et al. Does treatment delay predict occupational functioning in first-episode psychosis? Schizophrenia Research. 2007;91(1-3):259-62.
159. Penttila M, Haapea M, Koponen H, Veijola J, Miettunen J, Isohanni M, et al. Duration of untreated psychosis and its relation to outcome in schizophrenia within the Northern Finland 1966 Birth Cohort. International Clinical Psychopharmacology. 2011;26.
160. Large M, Nielssen O. Evidence for a relationship between the duration of untreated psychosis and the proportion of psychotic homicides prior to treatment. Social Psychiatry and Psychiatric Epidemiology. 2008;43(1):37-44.
161. Helgason L. Twenty years' follow-up of first psychiatric presentation for schizophrenia: what could have been prevented? Acta Psychiatrica Scandinavica. 1990;81(3):231-5.
162. Kaymak SU, Altintas M, Unsal D, Sevinc E, Gulec H. Effects of duration of untreated psychosis on the clinical course and neurocognitive features of schizophrenia. Asia-Pacific Psychiatry. 2012;4(1):40-7.
163. May P, Tuma, AH. Treatment of Schizophrenia. The British Journal of Psychiatry. 1965;111(475):503-10.

164. Wyatt RJ, Green MF, Tuma AH. Long-term morbidity associated with delayed treatment of first admission schizophrenic patients: a re-analysis of the Camarillo State Hospital data. Psychological Medicine. 1997;27(02):261-8.
165. May PAR, Tuma AH, Dixon WJ, Thiele DA, Kraude WH. Schizophrenia: A follow-up study of the results of five forms of treatment. Archives of General Psychiatry. 1981;38(7):776-84.
166. May PAR, Tuma AH, Yale C, Potepan P, Dixon WJ. Schizophrenia—a follow-up study of results of treatment: II. hospital stay over two to five years. Archives of General Psychiatry. 1976;33(4):481-6.
167. Loebel AD LJ, Alvir JM, Mayerhoff DI, Geisler SH, Szymanski SR. Duration of psychosis and outcome in first-episode schizophrenia. Am J Psychiatry. 1992;149(9):1183-8.
168. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: A critical review and meta-analysis. American Journal of Psychiatry. 2005;162(10):1785-804.
169. Royal College of Psychiatrists. Forensic Psychiatric Services. 2015 [cited 2015 08.09.15]; Available from: http://www.rcpsych.ac.uk/healthadvice/partnersincarecampaign/forensicpsychiatricservices.aspx .
170. Pollack S. WMG, Howard A.,Fireworker R.B.,Kane J.M. Clozapine reduces rehospitalization among schizophrenia patients. Psychopharmacology Bulletin. 1998;34(1):89-92.
171. Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. J Clin Psychiatry. 2013;74(10):957-65. Epub 2013/11/16.
172. Frankenburg FR, Zanarini MC, Cole JO, McElroy SL. Hospitalization rates among clozapine-treated patients: a prospective cost-benefit analysis. Annals of Clinical Psychiatry. 1992;4(4):247-50.
173. Blieden N, Flinders S, Hawkins K, Reid M, Alphs LD, Arfken CL. Health status and health care costs for publicly funded patients with schizophrenia started on clozapine. Psychiatr Serv. 1998;49(12):1590-3. Epub 1998/12/18.
174. Dickson RA, Dalby JT, Williams R, Warden SJ. Hospital days in clozapine-treated patients. Canadian journal of psychiatry Revue canadienne de psychiatrie. 1998;43(9):945-8. Epub 1998/11/24.
175. Ghaemi SN, Ziegler DM, Peachey TJ, Goodwin FK. Cost-Effectiveness of Clozapine Therapy for Severe Psychosis. Psychiatric Services. 1998;49(6):829-31.
176. Luchins DJ, Hanrahan P, Shinderman M, Lagios L, Fichtner CG. Initiating clozapine treatment in the outpatient clinic: service utilization and cost trends. Psychiatr Serv. 1998;49(8):1034-8. Epub 1998/08/26.
177. Faries DE, Nyhuis AW, Ascher-Svanum H. Methodological issues in assessing changes in costs pre- and post-medication switch: a schizophrenia study example. Cost Effectiveness and Resource Allocation : C/E. 2009;7:11-.
178. Drew LR, Hodgson DM, Griffiths KM. Clozapine in community practice: a 3-year follow-up study in the Australian Capital Territory. The Australian and New Zealand journal of psychiatry. 1999;33(5):667-75. Epub 1999/11/02.
179. Taylor D, Olofinjana O. Long-acting paliperidone palmitate - interim results of an observational study of its effect on hospitalization. Int Clin Psychopharmacol. 2014;29(4):229-34. Epub 2014/01/15.
180. Meltzer HYB, S.; Bastani, B.; and Ramirez, L.F. . Effects of six months of clozapine treatment on the quality of life of chronic schizophrenic patients. Hospital and Community Psychiatry. 1990;141:892-7.
181. Reid WH, Mason M. Psychiatric hospital utilization in patients treated with clozapine for up to 4.5 years in a state mental health care system. J Clin Psychiatry. 1998;59(4):189-94. Epub 1998/05/20.
182. Office for National Statistics. Census: Aggregate data (England and Wales). UK Data Service Census Support, downloaded from http://infuseukdataserviceacuk. 2011.
183. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. American Journal of Psychiatry. 2006;163(4):600-10.
184. Leucht S, Pitschel-Walz G, Abraham D, Kissling W. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to

conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. Schizophrenia Research. 1999;35(1):51-68.
185. Galuppi A, Turola MC, Nanni MG, Mazzoni P, Grassi L. Schizophrenia and quality of life: how important are symptoms and functioning? International journal of mental health systems. 2010;4:31. Epub 2010/12/15.
186. Knapp M. Schizophrenia costs and treatment cost-effectiveness. Acta Psychiatrica Scandinavica. 2000;102:15-8.
187. Gee SH, Shergill SS, Taylor DM. Factors associated with changes in hospitalisation in patients prescribed clozapine. Journal of Psychopharmacology. 2016;30(8):819-25.
188. Yilmaz Z, Zai CC, Hwang R, Mann S, Arenovich T, Remington G, et al. Antipsychotics, dopamine D(2) receptor occupancy and clinical improvement in schizophrenia: a meta-analysis. Schizophr Res. 2012;140(1-3):214-20. Epub 2012/07/17.
189. Wolkin A, Barouche F, Wolf AP, Rotrosen J, Fowler JS, Shiue CY, et al. Dopamine blockade and clinical response: evidence for two biological subgroups of schizophrenia. Am J Psychiatry. 1989;146(7):905-8. Epub 1989/07/01.
190. Carpenter Jr. W.T. ZJM, Vitrai J.,Volavka J. Hypothesis testing: Is clozapine's superior efficacy dependent on moderate D2 receptor occupancy? Biological Psychiatry. 1998;43(2):79-83.
191. Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD. Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. Am J Psychiatry. 2012;169(11):1203-10. Epub 2012/10/05.
192. Demjaha A, Egerton A, Murray RM, Kapur S, Howes OD, Stone JM, et al. Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. Biol Psychiatry. 2014;75(5):e11-3. Epub 2013/07/31.
193. Goldstein ME, Anderson VM, Pillai A, Kydd RR, Russell BR. Glutamatergic neurometabolites in clozapine-responsive and -resistant schizophrenia. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP). 2015;18(6). Epub 2015/01/22.
194. Agid O, Kapur S, Arenovich T, Zipursky RB. Delayed-onset hypothesis of antipsychotic action: A hypothesis tested and rejected. Archives of General Psychiatry. 2003;60(12):1228-35.
195. Leucht S, Busch R, Hamann J, Kissling W, Kane JM. Early-Onset Hypothesis of Antipsychotic Drug Action: A Hypothesis Tested, Confirmed and Extended. Biological Psychiatry. 2005;57(12):1543-9.
196. Correll CU, Malhotra AK, Kaushik S, McMeniman M, Kane JM. Early prediction of antipsychotic response in schizophrenia. Am J Psychiatry. 2003;160(11):2063-5. Epub 2003/11/05.
197. Waddington JL, Youssef HA, Kinsella A. Mortality in schizophrenia. Antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. Br J Psychiatry. 1998;173:325-9. Epub 1999/02/02.
198. Joukamaa M, Heliovaara M, Knekt P, Aromaa A, Raitasalo R, Lehtinen V. Schizophrenia, neuroleptic medication and mortality. Br J Psychiatry. 2006;188:122-7. Epub 2006/02/02.
199. Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P. Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. Archives of General Psychiatry. 2012;69(5):476-83.
200. Baandrup L, Gasse C, Jensen VD, Glenthoj BY, Nordentoft M, Lublin H, et al. Antipsychotic polypharmacy and risk of death from natural causes in patients with schizophrenia: a population-based nested case-control study. J Clin Psychiatry. 2010;71(2):103-8. Epub 2009/11/10.
201. Tiihonen J, Mittendorfer-Rutz E, Majak M, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia. JAMA psychiatry. 2017;74(7):686-93.
202. Barnes TR, Paton C. Antipsychotic polypharmacy in schizophrenia: benefits and risks. CNS Drugs. 2011;25(5):383-99. Epub 2011/04/12.
203. Patel MX, Bishara D, Jayakumar S, Zalewska K, Shiers D, Crawford MJ, et al. Quality of prescribing for schizophrenia: Evidence from a national audit in England and Wales. European Neuropsychopharmacology. 2014;24(4):499-509.
204. Nielsen J, Nielsen RE, Correll CU. Predictors of clozapine response in patients with treatment-refractory schizophrenia: results from a Danish Register Study. J Clin Psychopharmacol. 2012;32(5):678-83. Epub 2012/08/29.
205. Aleman A, Kahn RS, Selten J. Sex differences in the risk of schizophrenia: Evidence from meta-analysis. Archives of General Psychiatry. 2003;60(6):565-71.

206. Manteuffel M, Williams S, Chen W, Verbrugge RR, Pittman DG, Steinkellner A. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. Journal of women's health (2002). 2014;23(2):112-9. Epub 2013/11/12.
207. Chen SL, Lee WL, Liang T, Liao IC. Factors associated with gender differences in medication adherence: a longitudinal study. Journal of advanced nursing. 2014;70(9):2031-40. Epub 2014/02/11.
208. Todd P. Gilmer, Christian R. Dolder, Jonathan P. Lacro, David P. Folsom, Laurie Lindamer, Piedad Garcia, et al. Adherence to Treatment With Antipsychotic Medication and Health Care Costs Among Medicaid Beneficiaries With Schizophrenia. American Journal of Psychiatry. 2004;161(4):692-9.
209. Valenstein M, Blow FC, Copeland LA, McCarthy JF, Zeber JE, Gillon L, et al. Poor antipsychotic adherence among patients with schizophrenia: medication and patient factors. Schizophrenia Bulletin. 2004;30(2):255.
210. EM. W. Antipsychotic prescribing practices in the Veterans Healthcare Administration--New York metropolitan region. Schizophr Bull. 2002;28:31-42.
211. Correll CU, Shaikh L, Gallego JA, Nachbar J, Olshanskiy V, Kishimoto T, et al. Antipsychotic polypharmacy: A survey study of prescriber attitudes, knowledge and behavior. Schizophrenia Research. 2011;131(1):58-62.
212. O'Brien A, Firn M. Clozapine initiation in the community. Psychiatric Bulletin. 2002;26(9):339-41.
213. O'Brien A. Starting clozapine in the community: A UK perspective. CNS Drugs. 2004;18(13):845-52.
214. Beck K, McCutcheon R, Bloomfield MA, Gaughran F, Reis Marques T, MacCabe J, et al. The practical management of refractory schizophrenia--the Maudsley Treatment REview and Assessment Team service approach. Acta Psychiatr Scand. 2014;130(6):427-38. Epub 2014/09/10.
215. Fenton WS, Blyler CR, Heinssen RK. Determinants of Medication Compliance in Schizophrenia: Empirical and Clinical Findings. Schizophrenia Bulletin. 1997;23(4):637-51.
216. Van Putten T. Why do schizophrenic patients refuse to take their drugs? Archives of General Psychiatry. 1974;31(1):67-72.
217. Norell SE. Accuracy of patient interviews and estimates by clinical staff in determining medication compliance. Social Science & Medicine Part E: Medical Psychology. 1981;15(1):57-61.
218. McClellan TA, Cowan G. Use of antipsychotic and antidepressant drugs by chronically ill patients. Am J Psychiatry. 1970;126(12):1771-3. Epub 1970/06/01.
219. Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. Psychiatr Serv. 1998;49(2):196-201. Epub 1998/05/09.
220. Grover S, Balachander S, Chakarabarti S, Avasthi A. Prescription practices and attitude of psychiatrists towards clozapine: A survey of psychiatrists from India. Asian Journal of Psychiatry.18:57-65.
221. Cooper D, Moisan J, Gregoire JP. Adherence to atypical antipsychotic treatment among newly treated patients: a population-based study in schizophrenia. J Clin Psychiatry. 2007;68(6):818-25. Epub 2007/06/27.
222. Valevski A, Gilat Y, Olfson M, Benaroya-Milshtein N, Weizman A. Antipsychotic monotherapy and adjuvant psychotropic therapies in schizophrenia patients: effect on time to readmission. International Clinical Psychopharmacology. 2012;27(3):159-64 10.1097/YIC.0b013e328350ddbe.
223. Couchman L, Morgan PE, Spencer EP, Flanagan RJ. Plasma Clozapine, Norclozapine, and the Clozapine:Norclozapine Ratio in Relation to Prescribed Dose and Other Factors: Data From a Therapeutic Drug Monitoring Service, 1993–2007. Therapeutic Drug Monitoring. 2010;32(4):438-47.
224. Honigfeld Gea. Reducing clozapine related morbidity and mortality, 5 years experience with Clozaril National Registry. J Clin Psych. 1998;50(suppl 3):3-7.
225. Schulte PF. Risk of Clozapine-Associated Agranulocytosis and Mandatory White Blood Cell Monitoring. Annals of Pharmacotherapy. 2006;40(4):683-8.
226. Ingimarsson O, MacCabe JH, Haraldsson M, Jónsdóttir H, Sigurdsson E. Clozapine treatment and discontinuation in Iceland: A national longitudinal study using electronic patient records. Nordic Journal of Psychiatry. 2016;70(6):450-5.
227. Girardin FR, Poncet A, Blondon M, Rollason V, Vernaz N, Chalandon Y, et al. Monitoring white blood cell count in adult patients with schizophrenia who are taking clozapine: a cost-effectiveness analysis. The Lancet Psychiatry. 2014;1(1):55-62.

228. Ringbäck Weitoft G, Berglund M, Lindström EA, Nilsson M, Salmi P, Rosén M. Mortality, attempted suicide, re-hospitalisation and prescription refill for clozapine and other antipsychotics in Sweden—a register-based study. Pharmacoepidemiology and Drug Safety. 2014:n/a-n/a.
229. Land R, Siskind D, McArdle P, Kisely S, Winckel K, Hollingworth SA. The impact of clozapine on hospital use: a systematic review and meta-analysis. Acta Psychiatr Scand. 2017;135(4):296-309. Epub 2017/02/06.
230. Briggs C, Kimber S, Green L. Where are we at with point- of- care testing in haematology? British Journal of Haematology. 2012;158(6):679-90.
231. Nielsen J, Thode D, Stenager E, Andersen KØ, Sondrup U, Hansen TN, et al. Hematological clozapine monitoring with a point-of-care device: A randomized cross-over trial. European Neuropsychopharmacology. 2012;22(6):401-5.
232. Carruthers J, Radigan M, Erlich MD, Gu G, Wang R, Frimpong EY, et al. An Initiative to Improve Clozapine Prescribing in New York State. Psychiatr Serv. 2016;67(4):369-71. Epub 2016/01/05.
233. Leucht S. Psychiatric treatment guidelines: Doctor's non-compliance or insufficient evidence? Acta Psychiatrica Scandinavica. 2007;115(6):417-9.
234. National Institute for Health and Clinical Excellence. National Clinical Guideline 82: Schizophrenia (updated version). Leicester: British Psychological Society; 2010.
235. Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines in Psychiatry. 2015;12th Ed.
236. Qurashi I, Stephenson P, Chu S, Duffy C, Husain N, Chaudhry I. An evaluation of subjective experiences, effects and overall satisfaction with clozapine treatment in a UK forensic service. Ther Adv Psychopharmacol. 2015;5(3):146-50. Epub 2015/07/23.
237. Gonzalez C, Kodimela K, Poynton A. Clozapine initiation in crisis teams. British Journal of Medical Practitioners. 2013;6(2).
238. Rettenbacher MA, Burns T, Kemmler G, Fleischhacker WW. Schizophrenia: attitudes of patients and professional carers towards the illness and antipsychotic medication. Pharmacopsychiatry. 2004;37(3):103-9. Epub 2004/05/13.
239. Zita D.F. GJ. Helping clozapine help: a role for support groups. Schizophrenia Bulletin. 2002;28(1):123-6.
240. Miller BJ, Stewart A, Schrimsher J, Peeples D, Buckley PF. How connected are people with schizophrenia? Cell phone, computer, email, and social media use. Psychiatry Res. 2015;225(3):458-63. Epub 2015/01/08.
241. Baptist AP, Thompson M, Grossman KS, Mohammed L, Sy A, Sanders GM. Social media, text messaging, and email-preferences of asthma patients between 12 and 40 years old. The Journal of asthma : official journal of the Association for the Care of Asthma. 2011;48(8):824-30. Epub 2011/08/26.
242. Castelein S, Bruggeman R, Van Busschbach JT, Van Der Gaag M, Stant AD, Knegtering H, et al. The effectiveness of peer support groups in psychosis: a randomized controlled trial. Acta Psychiatrica Scandinavica. 2008;118(1):64-72.
243. Gianfrancesco F, Wang R-H, Mahmoud R, White R. Methods for Claims-Based Pharmacoeconomic Studies in Psychosis. PharmacoEconomics. 2002;20(8):499-511.
244. Aitchison KJ, Kerwin RW. Cost-effectiveness of clozapine. A UK clinic-based study. The British Journal of Psychiatry. 1997;171(2):125-30.
245. Rosenheck R, Evans D, Herz L, Cramer J, Xu W, Thomas J, et al. How long to wait for a response to clozapine: a comparison of time course of response to clozapine and conventional antipsychotic medication in refractory schizophrenia. Schizophr Bull. 1999;25(4):709-19. Epub 2000/02/10.
246. Bressington D, Stock J, Hulbert S, MacInnes D. A retrospective observational study of the effectiveness of paliperidone palmitate on acute inpatient hospitalization rates. Int Clin Psychopharmacol. 2015;30(4):230-6. Epub 2015/04/18.
247. Ahn YM, Chang JS, Kim Y, Lee KY, Kim JH, Kim SC, et al. Reduction in hospital stay of chronic schizophrenic patients after long-term clozapine treatment. Int Clin Psychopharmacol. 2005;20(3):157-61. Epub 2005/04/07.
248. Lieberman J, Safferman A, Pollack S, Szymanski S, Johns C, Howard A, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. American Journal of Psychiatry. 1994;151(12):1744-52.
249. Altamura AC, Bobo WV, Meltzer HY. Factors affecting outcome in schizophrenia and their relevance for psychopharmacological treatment. Int Clin Psychopharmacol. 2007;22(5):249-67. Epub 2007/08/11.

250. Köhler-Forsberg O, Horsdal HT, Legge SE, MacCabe JH, Gasse C. Predictors of Nonhospitalization and Functional Response in Clozapine Treatment: A Nationwide, Population-Based Cohort Study. Journal of Clinical Psychopharmacology. 2017;37(2):148-54.
251. Woerner MG, Robinson DG, Alvir JM, Sheitman BB, Lieberman JA, Kane JM. Clozapine as a first treatment for schizophrenia. Am J Psychiatry. 2003;160(8):1514-6. Epub 2003/08/06.
252. Meltzer HY, Bobo WV, Lee MA, Cola P, Jayathilake K. A randomized trial comparing clozapine and typical neuroleptic drugs in non-treatment-resistant schizophrenia. Psychiatry Research. 2010;177(3):286-93.
253. Lieberman JA, Phillips M, Gu H, Stroup S, Zhang P, Kong L, et al. Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2003;28(5):995-1003.
254. Tiihonen J. WK, Lonnqvist J.,Klaukka T.,Ioannidis J.P.A.,Volavka J.,Haukka J. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder. British Medical Journal. 2006;333(7561):224-7.
255. Taipale H, Mehtala J, Tanskanen A, Tiihonen J. Comparative Effectiveness of Antipsychotic Drugs for Rehospitalization in Schizophrenia-A Nationwide Study With 20-Year Follow-up. Schizophr Bull. 2017. Epub 2017/12/23.
256. Lambert T, Brennan A, Castle D, Kelly D, Conley R. Perception of Depot Antipsychotics by Mental Health Professionals. Journal of Psychiatric Practice®. 2003;9(3):252-60.
257. Darlow B, Fullen BM, Dean S, Hurley DA, Baxter GD, Dowell A. The association between health care professional attitudes and beliefs and the attitudes and beliefs, clinical management, and outcomes of patients with low back pain: a systematic review. European journal of pain (London, England). 2012;16(1):3-17. Epub 2011/07/02.
258. Greeman M, McClellan TA. Negative effects of a smoking ban on an inpatient psychiatry service. Hosp Community Psychiatry. 1991;42(4):408-12. Epub 1991/04/01.
259. Mace S, Taylor D. Reducing the rates of prescribing high-dose antipsychotics and polypharmacy on psychiatric inpatient and intensive care units: results of a 6-year quality improvement programme. Ther Adv Psychopharmacol. 2015;5(1):4-12. Epub 2015/02/06.
260. Lieberman JA, Kane JM, Safferman AZ, Pollack S, Howard A, Szymanski S, et al. Predictors of response to clozapine. J Clin Psychiatry. 1994;55 Suppl B:126-8. Epub 1994/09/01.
261. Umbricht DS, Wirshing WC, Wirshing DA, McMeniman M, Schooler NR, Marder SR, et al. Clinical predictors of response to clozapine treatment in ambulatory patients with schizophrenia. J Clin Psychiatry. 2002;63(5):420-4. Epub 2002/05/22.
262. Szymanski S, Lieberman J, Pollack S, Kane JM, Safferman A, Munne R, et al. Gender differences in neuroleptic nonresponsive clozapine-treated schizophrenics. Biol Psychiatry. 1996;39(4):249-54. Epub 1996/02/15.
263. Gee S, Vergunst F, Howes O, Taylor D. Practitioner attitudes to clozapine initiation. Acta Psychiatrica Scandinavica. 2014;130(1):16-24.
264. Schulte PF. Risk of clozapine-associated agranulocytosis and mandatory white blood cell monitoring. The Annals of pharmacotherapy. 2006;40(4):683-8. Epub 2006/04/06.
265. Kelly DL, Ben-Yoav H, Payne GF, Winkler TE, Chocron SE, Kim E, et al. Blood Draw Barriers for Treatment with Clozapine and Development of Point-of-Care Monitoring Device. Clin Schizophr Relat Psychoses. 2015.
266. Wolff J, McCrone P, Patel A, Kaier K, Normann C. Predictors of length of stay in psychiatry: analyses of electronic medical records. BMC Psychiatry. 2015;15(1):238.
267. Tungaraza TE, Farooq S. Clozapine prescribing in the UK: views and experience of consultant psychiatrists. Therapeutic Advances in Psychopharmacology. 2015;5(2):88-96.
268. Grassi B. FR, Epifani M.,Dragoni C.,Cohen S.,Scarone S. Clozapine lacks previous clinical efficacy when restarted after a period of discontinuation: A case series. European Neuropsychopharmacology. 1999;9(6):479-81.

Appendix A. Statistical data for chapter 2

Table 7-1 Z-scores

	Frequency	Percent	Valid Percent	Cumulative Percent
Extreme outliers (z-score > 3.29)	3	1.3	2.0	2.0
Probable outliers (z-score > 2.58)	1	.4	.7	2.7
Potential outliers (z-score > 1.96)	7	3.1	4.7	7.4
Normal range	138	61.6	92.6	100.0
Total	149	66.5	100.0	

Table 7-2 Kolomogorov-Smirnov and Shapiro-Wilk tests of normality

		Kolmogorov-Smirnov			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
Included patients	Age	0.105	149	< 0.0005	0.933	149	< 0.0005
	Sex	0.435	149	< 0.0005	0.585	149	< 0.0005
	Ethnicity	0.287	149	< 0.0005	0.762	149	< 0.0005
	Primary diagnosis	0.464	149	< 0.0005	0.539	149	< 0.0005
	Duration of Illness (years)	0.132	149	< 0.0005	0.888	149	< 0.0005
	Theoretical Delay (years)	0.217	149	< 0.0005	0.776	149	< 0.0005
Excluded patients	Age	0.121	75	0.008	0.956	75	0.010
	Sex	0.357	75	< 0.0005	0.635	75	< 0.0005
	Ethnicity	0.378	75	< 0.0005	0.706	75	< 0.0005
	Primary diagnosis	0.391	75	< 0.0005	0.669	75	< 0.0005
	Duration of Illness (years)	0.091	70	0.200	0.954	70	0.012

Table 7-3 Levene's test for homogeneity of variance

		Levene Statistic	df1	df2	Sig.
Age	Based on Mean	4.173	1	217	0.042
	Based on Median	3.222	1	217	0.074
	Based on Median and with adjusted df	3.222	1	207.940	0.074
	Based on trimmed mean	3.760	1	217	0.054
Sex	Based on Mean	10.290	1	217	0.002
	Based on Median	5.068	1	217	0.025
	Based on Median and with adjusted df	5.068	1	215.878	0.025
	Based on trimmed mean	10.290	1	217	0.002
Ethnicity	Based on Mean	0.136	1	217	0.713
	Based on Median	2.653	1	217	0.105
	Based on Median and with adjusted df	2.653	1	114.832	0.106
	Based on trimmed mean	0.472	1	217	0.493
Primary diagnosis	Based on Mean	26.524	1	217	<0.0005
	Based on Median	8.177	1	217	0.005
	Based on Median and with adjusted df	8.177	1	180.131	0.005
	Based on trimmed mean	22.829	1	217	<0.0005
Duration of Illness in years	Based on Mean	21.992	1	217	<0.0005
	Based on Median	18.902	1	217	<0.0005
	Based on Median and with adjusted df	18.902	1	182.928	<0.0005
	Based on trimmed mean	21.071	1	217	<0.0005

Table 7-4 Independent samples t-test for continuous variables, comparing included and excluded patient group means

	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Diff.	Std. error	95% Confidence Interval	
								Lower	Upper
Age									
Equal variances assumed	4.173	0.042	-5.436	217	<0.0005	-8.764	1.612	-11.941	-5.586
Equal variances not assumed			-5.017	111.874	<0.0005	-8.764	1.747	-12.225	-5.303
Duration of Illness in years									
Equal variances assumed	21.992	<0.0005	-7.883	217	<0.0005	-7.837	0.994	-9.797	-5.878
Equal variances not assumed			-6.612	92.487	<0.0005	-7.837	1.185	-10.191	-5.483

Table 7-5 Bootstrap for independent samples t-test

	Mean Difference	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Age						
Equal variances assumed	-8.764	0.010	1.773	0.001	-12.217	-5.379
Equal variances not assumed	-8.764	0.010	1.773	0.001	-12.217	-5.379
Duration of Illness in years						
Equal variances assumed	-7.837	-0.005	1.101	0.001	-10.000	-5.752
Equal variances not assumed	-7.837	-0.005	1.101	0.001	-10.000	-5.752

Table 7-6 Chi-square test for continuous variable of gender, comparing included and excluded patient groups

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.917	1	0.027		
Continuity Correction	4.287	1	0.038		
Likelihood Ratio	4.854	1	0.028		
Fisher's Exact Test				0.029	0.020
Linear-by-Linear Association	4.895	1	0.027		
N of Valid Cases	224				

0 cells (0.0%) have expected count less than 5. The minimum expected count is 27.46.

Table 7-7 Chi-square test for continuous variable of ethnicity, comparing included and excluded patient groups

	Value	**df**	**Asymp. Sig. (2-sided)**	**Exact Sig. (2-sided)**	**Exact Sig. (1-sided)**	**Point Probability**
Pearson Chi-Square	12.121	5	0.033	0.024		
Likelihood Ratio	12.759	5	0.026	0.031		
Fisher's Exact Test	11.719			0.026		
Linear-by-Linear Association	5.199	1	0.023	0.023	0.012	0.003
N of Valid Cases	224					

5 cells (41.7%) have expected count less than 5. The minimum expected count is 0.33.

Table 7-8 Crosstabulation for ethnicity of included compared to excluded patient groups

		Included patients	Excluded patients	Total
White	Count	61$_a$	45$_b$	106
	Expected Count	70.5	35.5	106.0
	% within Ethnicity	57.5%	42.5%	100.0%
	% within Included / Excluded	40.9%	60.0%	47.3%
	% of Total	27.2%	20.1%	47.3%
	Std. Residual	-1.1	1.6	
Mixed race	Count	12$_a$	2$_a$	14
	Expected Count	9.3	4.7	14.0
	% within Ethnicity	85.7%	14.3%	100.0%
	% within Included / Excluded	8.1%	2.7%	6.3%
	% of Total	5.4%	0.9%	6.3%
	Std. Residual	0.9	-1.2	
Asian and Asian British	Count	7$_a$	5$_a$	12
	Expected Count	8.0	4.0	12.0
	% within Ethnicity	58.3%	41.7%	100.0%
	% within Included / Excluded	4.7%	6.7%	5.4%
	% of Total	3.1%	2.2%	5.4%
	Std. Residual	-0.3	0.5	
Black or Black British	Count	61$_a$	20$_b$	81
	Expected Count	53.9	27.1	81.0
	% within Ethnicity	75.3%	24.7%	100.0%
	% within Included / Excluded	40.9%	26.7%	36.2%
	% of Total	27.2%	8.9%	36.2%
	Std. Residual	1.0	-1.4	
Other Ethnic Category	Count	8$_a$	2$_a$	10
	Expected Count	6.7	3.3	10.0
	% within Ethnicity	80.0%	20.0%	100.0%
	% within Included / Excluded	5.4%	2.7%	4.5%
	% of Total	3.6%	0.9%	4.5%
	Std. Residual	0.5	-0.7	
Not Stated	Count	0$_a$	1$_a$	1
	Expected Count	0.7	0.3	1.0
	% within Ethnicity	0.0%	100.0%	100.0%
	% within Included / Excluded	0.0%	1.3%	0.4%
	% of Total	0.0%	0.4%	0.4%
	Std. Residual	-0.8	1.1	
Total	Count	149	75	224
	Expected Count	149.0	75.0	224.0
	% within Ethnicity	66.5%	33.5%	100.0%
	% within Included / Excluded	100.0%	100.0%	100.0%
	% of Total	66.5%	33.5%	100.0%

Each subscript letter denotes a subset of Included / Excluded categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 7-9 Crosstabulation for ethnicity of included compared to excluded patient groups, merged categories

		Included patients	Excluded patients	Total
White	Count	61_a	45_b	106
	Expected Count	70.5	35.5	106.0
	% within Ethnicity	57.5%	42.5%	100.0%
	% within Included / Excluded	40.9%	60.0%	47.3%
	% of Total	27.2%	20.1%	47.3%
	Std. Residual	-1.1	1.6	
Black	Count	61_a	20_b	81
	Expected Count	53.9	27.1	81.0
	% within Ethnicity	75.3%	24.7%	100.0%
	% within Included / Excluded	40.9%	26.7%	36.2%
	% of Total	27.2%	8.9%	36.2%
	Std. Residual	1.0	-1.4	
Other	Count	27_a	10_a	37
	Expected Count	24.6	12.4	37.0
	% within Ethnicity	73.0%	27.0%	100.0%
	% within Included / Excluded	18.1%	13.3%	16.5%
	% of Total	12.1%	4.5%	16.5%
	Std. Residual	0.5	-0.7	
Total	Count	149	75	224
	Expected Count	149.0	75.0	224.0
	% within Ethnicity	66.5%	33.5%	100.0%
	% within Included / Excluded	100.0%	100.0%	100.0%
	% of Total	66.5%	33.5%	100.0%

Each subscript letter denotes a subset of Included / Excluded categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 7-10 Chi-square test for continuous variable of ethnicity, comparing included and excluded patient groups, categories merged

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Pearson Chi-Square	7.333	2	0.026	0.025		
Likelihood Ratio	7.369	2	0.025	0.027		
Fisher's Exact Test	7.190			0.027		
Linear-by-Linear Association	5.197	1	0.023	0.027	0.014	0.006
N of Valid Cases	224					

0 cells (0.0%) have expected count less than 5. The minimum expected count is 12.39.

Table 7-11 Chi-square test for continuous variable of diagnosis, comparing included and excluded patient groups

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	10.647	3	0.014
Likelihood Ratio	10.144	3	0.017
Linear-by-Linear Association	8.741	1	0.003
N of Valid Cases	224		

2 cells (25.0%) have expected count less than 5. The minimum expected count is 2.01.

Table 7-12 Crosstabulation for diagnosis of included compared to excluded patient groups

		Included patients	Excluded patients	Total
Schizophrenia	Count	116_a	49_b	165
	Expected Count	109.8	55.2	165.0
	% within diagnosis	70.3%	29.7%	100.0%
	% within Included / Excluded	77.9%	65.3%	73.7%
	% of Total	51.8%	21.9%	73.7%
	Std. Residual	0.6	-0.8	
Schizoaffective Disorder	Count	24_a	12_a	36
	Expected Count	23.9	12.1	36.0
	% within diagnosis	66.7%	33.3%	100.0%
	% within Included / Excluded	16.1%	16.0%	16.1%
	% of Total	10.7%	5.4%	16.1%
	Std. Residual	0	0	
Bipolar Disorder	Count	8_a	9_a	17
	Expected Count	11.3	5.7	17.0
	% within diagnosis	47.1%	52.9%	100.0%
	% within Included / Excluded	5.4%	12.0%	7.6%
	% of Total	3.6%	4.0%	7.6%
	Std. Residual	-1.0	1.4	
Other	Count	1_a	5_b	6
	Expected Count	4.0	2.0	6.0
	% within diagnosis	16.7%	83.3%	100.0%
	% within Included / Excluded	0.7%	6.7%	2.7%
	% of Total	0.4%	2.2%	2.7%
	Std. Residual	-1.5	2.1	
Total	Count	149	75	224
	Expected Count	149.0	75.0	224.0
	% within Primary diagnosis	66.5%	33.5%	100.0%
	% within Included / Excluded	100.0%	100.0%	100.0%
	% of Total	66.5%	33.5%	100.0%

Each subscript letter denotes a subset of Included / Excluded categories whose column proportions do not differ significantly from each other at the 0.05 level

Table 7-13 Crosstabulation for diagnosis of included compared to excluded patient groups, merged categories

		Included patients	Excluded patients	Total
Schizophrenia	Count	116_a	49_b	165
	Expected Count	109.8	55.2	165.0
	% within Diagnosis	70.3%	29.7%	100.0%
	% within Included / Excluded	77.9%	65.3%	73.7%
	% of Total	51.8%	21.9%	73.7%
	Std. Residual	0.6	-0.8	
Schizoaffective disorder	Count	24_a	12_a	36
	Expected Count	23.9	12.1	36.0
	% within Diagnosis	66.7%	33.3%	100.0%
	% within Included / Excluded	16.1%	16.0%	16.1%
	% of Total	10.7%	5.4%	16.1%
	Std. Residual	0	0	
Other	Count	9_a	14_b	23
	Expected Count	15.3	7.7	23.0
	% within Diagnosis	39.1%	60.9%	100.0%
	% within Included / Excluded	6.0%	18.7%	10.3%
	% of Total	4.0%	6.3%	10.3%
	Std. Residual	-1.6	2.3	
Total	Count	149	75	224
	Expected Count	149.0	75.0	224.0
	% within Diagnosis	66.5%	33.5%	100.0%
	% within Included / Excluded	100.0%	100.0%	100.0%
	% of Total	66.5%	33.5%	100.0%

Each subscript letter denotes a subset of Included / Excluded categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 7-14 Chi-square test for continuous variable of diagnosis, comparing included and excluded patient groups, categories merged

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Pearson Chi-Square	8.808	2	0.012	0.012		
Likelihood Ratio	8.269	2	0.016	0.020		
Fisher's Exact Test	8.310			0.016		
Linear-by-Linear Association	7.179	1	0.007	0.008	0.006	0.003
N of Valid Cases	224					

0 cells (0.0%) have expected count less than 5. The minimum expected count is 7.70.

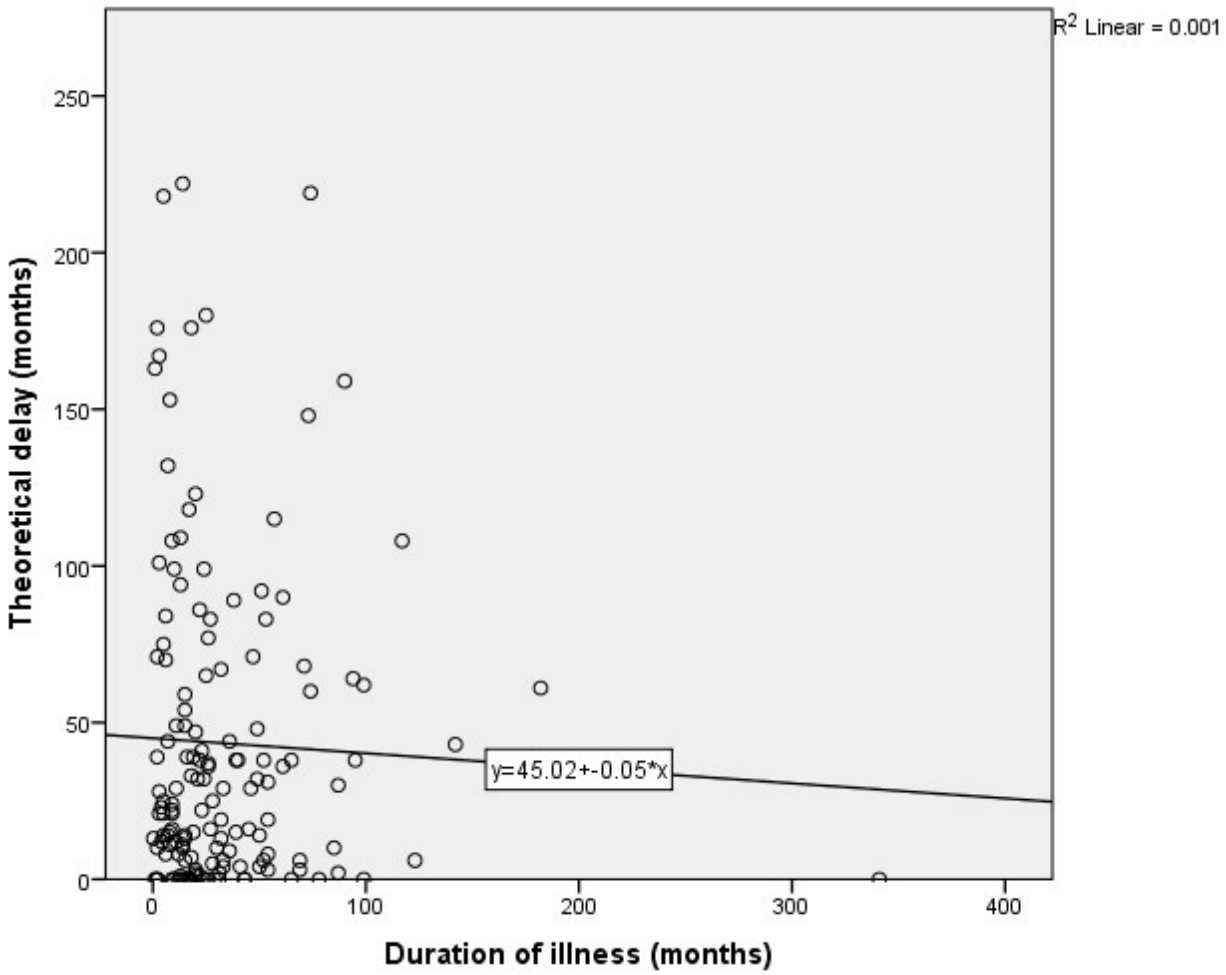

Figure 7-1 Relationship between theoretical delay to clozapine initiation and duration of the illness

Table 7-15 Regression model summary (duration of illness)

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.037	0.001	-0.005	51.109

Table 7-16 ANOVA (duration of illness)

	Sum of Squares	df	Mean Square	F	Sig.
Regression	537.729	1	537.729	0.206	0.651
Residual	383977.224	147	2612.090		
Total	384514.953	148			

Table 7-17 Model coefficients (duration of illness)

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	45.015	5.530		8.140	<0.0005
Duration of illness (months)	-0.048	0.106	-0.037	-0.454	0.651

Table 7-18 Bootstrap for model coefficients (duration of illness)

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	95% Confidence Interval	
					Lower	Upper
Constant	45.015	-0.762	5.781	0.001	32.456	55.782
Duration of illness (months)	-0.048	0.020	0.116	0.635	-0.227	0.243

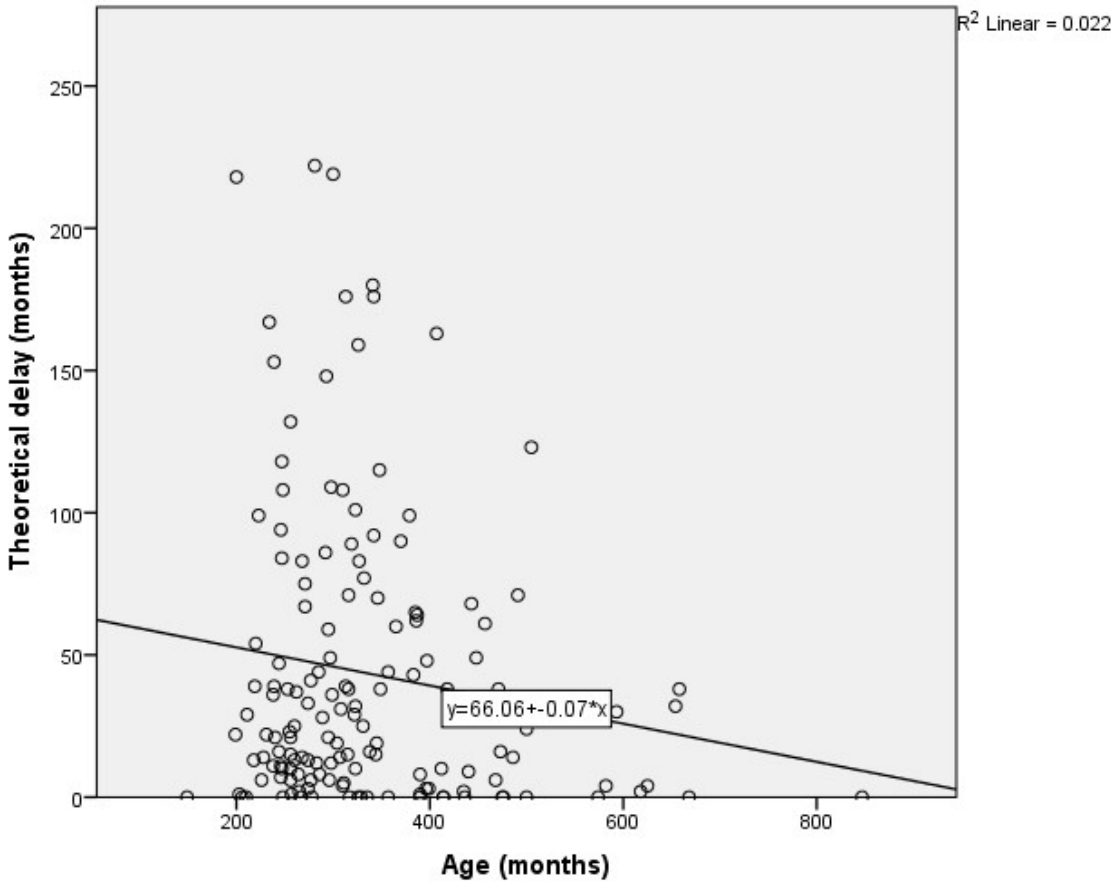

Figure 7-2 Relationship between theoretical delay to clozapine initiation and age

Table 7-19 Regression model summary (age)

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.147	0.022	0.015	50.590

Table 7-20 ANOVA (age)

	Sum of Squares	df	Mean Square	F	Sig.
Regression	8288.314	1	8288.314	3.238	0.074
Residual	376226.639	147	2559.365		
Total	384514.953	148			

Table 7-21 Model coefficients (age)

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	66.055	13.267		4.979	<0.0005
Age (months)	-0.067	0.037	-0.147	-1.800	0.074

Table 7-22 Bootstrap for model coefficients (age)

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	95% Confidence Interval	
					Lower	Upper
Constant	66.055	0.190	11.904	0.001	44.154	91.316
Age (months)	-0.067	-3.133E-5	0.028	0.016	-0.126	-0.011

Table 7-23 Multiple regression analysis model summary

	R	R^2	Adjusted R^2	Std. Error	Change Statistics					DurbinWatson
					R^2	F	df1	df2	Sig. F	
Model 1	0.147	0.022	0.015	50.590	0.022	3.238	1	147	0.074	
Model 2	0.147	0.022	0.008	50.760	<0.0005	0.015	1	146	0.902	1.740

Table 7-24 Levene's test for homogeneity of variance for ANCOVA

F	df1	df2	Sig.
2.019	67	81	0.001

Table 7-25 ANCOVA

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	139923.799	68	2057.703	0.673	0.953
Intercept	27246.679	1	27246.679	8.192	0.004
Age	2089.929	1	2089.929	0.684	0.411
Duration of illness	131635.485	67	1964.709	0.643	0.968
Error	244591.154	80	3057.389		
Total	664853.000	149			
Corrected Total	384514.953	148			

Table 7-26 Levene's test for homogeneity of variance for ANCOVA

F	df1	df2	Sig.
2.445	115	33	0.002

Table 7-27 ANCOVA

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	302452.699	116	2607.351	1.017	0.498
Intercept	77365.460	1	77365.460	30.168	<0.0005
Duration of illness	157.712	1	157.712	0.061	0.806
Age	301914.969	115	2625.348	1.024	0.488
Error	82062.254	32	2564.445		
Total	664853.000	149			
Corrected Total	384514.953	148			

Table 7-28 Independent samples t-test results (gender)

	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Diff.	Std. error	95% Confidence Interval of the Difference	
								Lower	Upper
Equal variances assumed	12.905	<0.0005	-2.792	147	0.006	-24.537	8.787	-41.902	-7.171
Equal variances not assumed			-2.435	66.408	0.018	-24.537	10.077	-44.653	-4.421

Table 7-29 Bootstrap for independent samples t-test (gender)

	Mean Difference	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Equal variances assumed	-24.537	0.057	9.849	0.018	-44.502	-5.927
Equal variances not assumed	-24.537	0.057	9.849	0.021	-44.502	-5.927

Table 7-30 Levene's test for homogeneity of variance (ethnicity)

Levene Statistic	df1	df2	Sig.
0.725	2	146	0.486

Table 7-31 ANOVA (ethnicity)

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	2553.194	2	1276.597	0.488	0.615
Within Groups	382023.692	146	2616.601		
Total	384576.886	148			

Table 7-32 ANOVA post-hoc tests (ethnicity)

	Ethnicity		Mean Difference	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Tukey HSD	White	Black	-3.443	9.262	0.927	-25.37	18.49
		Other	8.236	11.824	0.766	-19.76	36.23
	Black	White	3.443	9.262	0.927	-18.49	25.37
		Other	11.678	11.824	0.586	-16.32	39.68
	Other	White	-8.236	11.824	0.766	-36.23	19.76
		Black	-11.678	11.824	0.586	-39.68	16.32
Gabriel	White	Black	-3.443	9.262	0.976	-25.81	18.92
		Other	8.236	11.824	0.857	-19.75	36.22
	Black	White	3.443	9.262	0.976	-18.92	25.81
		Other	11.678	11.824	0.677	-16.31	39.67
	Other	White	-8.236	11.824	0.857	-36.22	19.75
		Black	-11.678	11.824	0.677	-39.67	16.31
Games-Howell	White	Black	-3.443	9.656	0.932	-26.36	19.47
		Other	8.236	10.448	0.711	-16.79	33.26
	Black	White	3.443	9.656	0.932	-19.47	26.36
		Other	11.678	10.016	0.478	-12.36	35.72
	Other	White	-8.236	10.448	0.711	-33.26	16.79
		Black	-11.678	10.016	0.478	-35.72	12.36

Table 7-33 Levene's test for homogeneity of variance (diagnosis)

Levene Statistic	df1	df2	Sig.
0.798	2	146	0.452

Table 7-34 ANOVA (diagnosis)

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	8002.128	2	4001.064	1.551	0.215
Within Groups	376574.758	146	2579.279		
Total	384576.886	148			

Table 7-35 ANOVA post-hoc tests (diagnosis)

	Diagnosis		Mean Difference	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Tukey HSD	Schizophrenia	Schizoaffective disorder	0.731	11.389	0.998	-26.24	27.70
		Other	-30.616	17.573	0.193	-72.23	11.00
	Schizoaffective disorder	Schizophrenia	-0.731	11.389	0.998	-27.70	26.24
		Other	-31.347	19.851	0.258	-78.35	15.66
	Other	Schizophrenia	30.616	17.573	0.193	-11.00	72.23
		Schizoaffective disorder	31.347	19.851	0.258	-15.66	78.35
Gabriel	Schizophrenia	Schizoaffective disorder	0.731	11.389	1.000	-25.02	26.48
		Other	-30.616	17.573	0.135	-67.57	6.34
	Schizoaffective disorder	Schizophrenia	-0.731	11.389	1.000	-26.48	25.02
		Other	-31.347	19.851	0.286	-77.95	15.25
	Other	Schizophrenia	30.616	17.573	0.135	-6.34	67.57
		Schizoaffective disorder	31.347	19.851	0.286	-15.25	77.95
Games-Howell	Schizophrenia	Schizoaffective disorder	0.731	9.475	0.997	-22.29	23.76
		Other	-30.616	17.104	0.224	-77.92	16.68
	Schizoaffective disorder	Schizophrenia	-0.731	9.475	0.997	-23.76	22.29
		Other	-31.347	18.281	0.239	-80.04	17.35
	Other	Schizophrenia	30.616	17.104	0.224	-16.68	77.92
		Schizoaffective disorder	31.347	18.281	0.239	-17.35	80.04

Appendix B. Practitioner attitudes to clozapine initiation: questionnaire

Practitioner attitudes to clozapine initiation

South London and Maudsley NHS Foundation Trust | Institute of Psychiatry at The Maudsley | King's College London

Please note:

- All questionnaires are **anonymous**
- Please **circle** the appropriate answer
- Please enter **TODAY'S DATE**: ……

1. PROFESSIONAL STATUS: (circle any that apply)

A. Care coordinator **B.** Nurse **C.** Consultant Psychiatrist **D.** Trainee Psychiatrist

E. Occupational Therapist **F.** Social Worker **G.** Pharmacist

H. Other (please specify) ……..

2. Please give your main ward / community location:……

3. GENDER: Male / Female

4. What is your AGE bracket: **18-25** years **26-35** years **36-45** years **46-55** years **56+** years

5. How familiar are you with the NICE guidelines relating to treatment resistant schizophrenia?

A. Not at all **B.** A little **C.** Fairly **D.** Very familiar

6. How familiar are you with methods for the initiation of clozapine treatment?

A. Not at all **B.** A little **C.** Fairly **D.** Very familiar

7. Approximately how many patients currently under your care are receiving clozapine, if any?

A. ……patients **B.** Don't know

8. I have been responsible for authorising/supporting clozapine initiation and titration: (circle ONE)

A. Within the last 6 months
B. Within the last year
C. More than a year ago
D. Never

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9. How would you rate clozapine's effectiveness in treating schizophrenia compared with other antipsychotics?

1	2	3	4	5	6	7	8	9	10
Much less effective				About the same			Much more effective		

10. In terms of treatment satisfaction, how satisfied do you believe patients treated with clozapine are, compared with patients treated with other (atypical) antipsychotics?

A. Much less satisfied **B.** Somewhat less satisfied **C.** Somewhat more satisfied **D.** Much more satisfied

11. In your team / workplace, would additional clinical and/or administrative resources facilitate the initiation of clozapine?

YES / NO

12. When would you typically consider authorising / supporting the initiation of clozapine treatment?

A. As first line treatment
B. After ONE adequate antipsychotic trial
C. After TWO adequate antipsychotic trials
D. After THREE adequate antipsychotic trials
E. After FOUR or more adequate antipsychotic trials
F. Don't know

13. Approximately what percentage of patients under your care who are eligible for clozapine are not currently receiving clozapine?

A. 0-20%
B. 21-40%
C. 41-60%
D. 61-80%
E. 81-100%
F. Don't know

PLEASE TURN OVER →

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South London and Maudsley NHS Foundation Trust | Institute of Psychiatry at The Maudsley | King's College London

14. In your opinion, how frequently do the following **patient factors** lead to delays in the initiation of clozapine once clozapine treatment is indicated?

A. Refusal / reticence about obtaining baseline blood tests

1. Infrequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

B. Refusal / reticence about regular blood monitoring

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

C. Refusal / reticence due to need for hospital admission for titration

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

D. Patient unconvinced about clozapine's efficacy

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

E. Patient concerned about tolerability

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

F. Significant medical factors / complications

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

G. Other (please specify)

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

15. How frequently do the following factors delay **you** from initiating / supporting clozapine titration in patients eligible for treatment?

A. Administrative (e.g. time taken to register with ZTAS)

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

B. Obtaining baseline blood tests

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

C. Staff resources (e.g. lack of staff to monitor clozapine)

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

D. Need for hospital admission (e.g. delays in obtaining an admission)

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

E. Cost of clozapine medication

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

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[15. continued: How frequently do the following factors delay **you** from initiating / supporting clozapine titration in patients eligible for treatment?]

F. Concerns about tolerability

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

G. Significant medical factors / complications

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

H. Other (please specify).....

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

16. In your opinion, how helpful would the following factors be in terms of facilitating the initiation of clozapine, were they available?

A. Additional administrative support (e.g. patient registration)

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

B. Additional staff dedicated to obtaining baseline blood tests

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

C. Dedicated hospital beds to enable initiation of clozapine as an in-patient

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

D. Dedicated staff to arrange and monitor the initiation of clozapine as an out-patient

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

E. Dedicated day-hospital placements to initiate clozapine as an out-patient

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

F. Other (please specify) .....

1. Not frequently **2.** Somewhat frequently **3.** Fairly frequently **4.** Very frequently **5.** Don't know

THANK YOU

Please add any additional comments here:

.....

.....

.....

.....

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Appendix C. Statistical data for chapter 3

Table 7-36 Mann-Whitney test statistics for clozapine familiarity and effectiveness questions

	Professional status	Sum of Ranks	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
How familiar are you with the NICE guidelines relating to treatment resistant schizophrenia?	Doctor	3697.50	537.500	3697.500	-2.930	0.003
	Pharmacy staff	1453.50				
	Total					
How familiar are you with methods for the initiation of clozapine treatment?	Doctor	3870.50	630.500	3870.500	-2.518	0.012
	Pharmacy staff	1485.50				
	Total					
How would you rate clozapine's effectiveness in treating schizophrenia compared with other antipsychotics?	Doctor	3828.00	747.000	3828.000	-1.278	0.201
	Pharmacy staff	1323.00				
	Total					
In terms of treatment satisfaction, how satisfied do you believe patients treated with clozapine are, compared with patients treated with other (atypical) antipsychotics?	Doctor	3603.00	828.000	3603.000	-0.245	0.806
	Pharmacy staff	1150.00				
	Total					

Table 7-37 Mann-Whitney test statistics for patient factor questions

Patient factor	Professional status	Sum of Ranks	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
Refusal/reticence about obtaining baseline blood tests	Doctor	3559.50	769.500	1000.500	-0.070	0.944
	Pharmacy staff	1000.50				
	Total					
Refusal/reticence about regular blood monitoring	Doctor	3674.50	750.500	981.500	-0.344	0.731
	Pharmacy staff	981.50				
	Total					
Refusal/reticence due to need for hospital admission for titration	Doctor	2521.00	362.000	482.000	-1.386	0.166
	Pharmacy staff	482.00				
	Total					
Patient unconvinced about clozapine's efficacy	Doctor	3308.00	526.000	697.000	-1.214	0.225
	Pharmacy staff	697.00				
	Total					
Patient concerned about tolerability	Doctor	3497.00	722.000	3497.000	-0.173	0.862
	Pharmacy staff	968.00				
	Total					
Significant medical factors/complications	Doctor	3372.50	597.500	3372.500	-0.334	0.738
	Pharmacy staff	813.50				
	Total					

Table 7-38 Mann-Whitney test statistics for staff factor questions

Staff factor	Professional status	Sum of Ranks	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
Administrative	Doctor	3112.00	697.000	3112.000	-0.318	0.751
	Pharmacy staff	983.00				
	Total					
Obtaining baseline blood tests	Doctor	3134.00	661.000	871.000	-0.302	0.762
	Pharmacy staff	871.00				
	Total					
Staff resources	Doctor	3014.50	555.500	726.500	-0.701	0.483
	Pharmacy staff	726.50				
	Total					
Need for hospital admission	Doctor	1810.00	310.000	401.000	-0.649	0.516
	Pharmacy staff	401.00				
	Total					
Cost of clozapine medication	Doctor	2740.00	620.000	830.000	-0.795	0.426
	Pharmacy staff	830.00				
	Total					
Concerns about tolerability	Doctor	3233.00	493.000	683.000	-1.752	0.080
	Pharmacy staff	683.00				
	Total					
Significant medical factors/compliance	Doctor	3112.00	683.000	893.000	-0.072	0.942
	Pharmacy staff	893.00				
	Total					

Table 7-39 Mann-Whitney test statistics for enabling factor questions

Enabling factor	Professional status	Sum of Ranks	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
Additional administrative support	Doctor	3138.00	500.000	690.000	-1.568	0.117
	Pharmacy staff	690.00				
	Total					
Additional staff dedicated to obtaining baseline blood tests	Doctor	3212.00	583.000	793.000	-1.092	0.275
	Pharmacy staff	793.00				
	Total					
Dedicated hospital beds to enable initiation of clozapine as an inpatient	Doctor	2296.50	343.500	2296.500	-0.864	0.388
	Pharmacy staff	553.50				
	Total					
Dedicated staff to arrange and monitor the initiation of clozapine as an outpatient	Doctor	2779.00	554.000	707.000	-0.083	0.934
	Pharmacy staff	707.00				
	Total					
Dedicated day-hospital placements to initiate clozapine as an outpatient	Doctor	2586.50	563.500	734.500	-0.042	0.967
	Pharmacy staff	734.50				
	Total					

Appendix D. Practitioner attitudes to clozapine initiation: free text comments

Table 7-40 Free-text responses to 'In your opinion, how frequently do the following patient factors lead to delays in the initiation of clozapine once clozapine treatment is indicated?'

Comment
Tolerability and side effects are a huge worry for patients who, from my experience, do not feel that this is seen as an important point when compared to reasons for starting clozapine
Even though patients refuse obtaining blood monitoring faily [*sic*] frequent [*sic*], the staff continue to work really hard in negotating [*sic*] with the patient, exploring reasons for refusal and offering support and reassurance
TB medication is less effective on clozapine - i [*sic*] remember that being an issue for one of my clients
Patients often lack insight into illness so do not want any treatment at all don't mind a treatment requiring blood tests
Weight gain seems to be a regular concern for patients and in addition some concerns such as hypersalivation and constipation
Relatives not keen on clozapine
No beds available to admit to start titration
Prescribers' lack of confidence in prescribing clozapine
Patient fears about side effects of medication - Fairly frequently
Influence of concerns about above factors from parents/carers
Low baseline neutorphil [*sic*] count - somewhat frequently
Expedient discharge - very frequently
Side effect profile
Unpleasant scary side effects involving heart racing etc. Need for monitoring makes it look 'scary'
Pharmacy's hilariously inflexible approach to dispensing clozapine when patients do not turn up as expected or out of hours etc. causes many cases requiring retitration [*sic*], bearing in mind most patients are admitted out of hours
Alcohol intake, likely to disengage: somewhat frequently

Table 7-41 Free-text responses to 'How frequently do the following factors delay you from initiating/supporting clozapine titration in patients eligible for treatment?'

Comment
Not really involved in Clozapine [*sic*] initiation
Obtaining bloods on a regular basis (rather than only baseline bloods) may be sometimes an issue
We are a specialist unit for clozapine re-titration so our experience will be atypical
Inability to impose a clozapine trial on certain patients, where all else have failed and patient remains floridly symptomatic and poses risks to self and others.
Young age
Management in community - somewhat frequently
Pharmacy's management of clozapine dispensing

Table 7-42 Free-text responses to 'In your opinion, how helpful would the following factors be in terms of facilitating the initiation of clozapine, were they available?'

	Comment
1	More support for patients around decision making, including preparing for potential side effects in advance
2	Please note- these questions are not applicable to Spring Ward
3	Waiting list may affect initaiting [*sic*] clozaping [*sic*] once the need has been identified
4	Dedicated clozapine team would be highly beneficial
5	Working within CAMHS would be helpful to know whether any such dedicated resources would be available to under 18s, aalthough [*sic*] numbers obviously very small
6	Information/adverts/leaflets - very frequently
7	Promotion of clozapine to patient and carers
8	Additional staff dedicated to obtaining baseline blood tests is super important. CT3 doctors of min 5 years training should not be routinely phlebotomy (see RCPsych guildeine [*sic*])

Table 7-43 Additional comments

	Comment
1	Home Treatment Team accept patients for titration but the initiation or the registration is done by the referring team
2	I assume that clinical psychologists are not your target population for completion of this survey and apologies for the regular 'don't know' responses. I do feel that, due to the nature of clients needing clozapine, the issue of tolerability etc is taken lightly by the team and more discussion in advance would improve compliance.
3	ZTAS are paid to look after the administrative and monitoring side of Clozapine [*sic*], and for the most part, take responsibility for this. No clinician should be dissuaded from use of Clozapine [*sic*] for administrative/logistical reasons
4	This is a disappointing questionnaire with too many leading questions
5	There have been three sudden, and unclear deaths of patients on Clozapine [*sic*] in the team I have worked with (over 2 or so years). It is not clear to me the monitoring processes indicated any risk. I think there are increasingly 'unsaid' fears amongst staff about this medication, which are not helped by a lack of transparency about how such deaths are reported and what the processes are for analysing the data nationally. I think this is an unidentified and little spoken about 'Practitioner Attitude' I am aware of locally (i.e. amongst non-psychiatry members of the MDT), that I hope it is helpful to highlight in this survey.
6	Caring for pts with depression, so this has been rarely a drug of choice in the area I'm currently working in
7	As a Care Coordinator working in a community setting I have seen clozapine improve the quality of some of my service users. I have seen one client who responded so well to clozapine that her quality of life changed so much. Unforunately [*sic*] she gained approx. 8 stone and she satopped [*sic*] the clozapine. She was prescribed orlistat but she wass [*sic*] unable to tolerate it. Our team is now down to 8 members and it will be very difficult to commite [*sic*] to community clozapine tritration [*sic*]
8	We have considerable experience of treating patients who did not respond to clozapine monotherapy and were augmented by another atypical antipsychotic medication
9	Difficult for me to comment, as so rarely used in adolescents. My reservation would be such a serious undertaking in ones so young
10	Tricky medication requiring a lot of input in terms of monitoring physical effects, particularly patients in the community
11	Having only experience of 1 -2 patients on clozapine, I am not an expert or clinician, being a social worker in mental health. However, effects have been good
12	Courier times a significant problem with a chaotic group - eg. Arrive too late and courier 'gone'
13	More information for SHOs RE benign ethnic neutropaenia, which can cause anxiety and 'amber' results for FBC
14	I don't feel this survey is very applicable to me, especially working in an older adult ward. I'm not really exposed to the various problems that this survey alludes to
15	Patient yesterday admitted described clozapine as a wonder drug for him, reduction in negative symptoms, clozapine 'makes me do things'
16	Unfortunately, I have always worked as inpatient, so no outpaitne [*sic*] information I am aware of

Appendix E. Patient attitudes to clozapine: questionnaire

Patient code number:

Date:

Demographics:

- Age:
- Gender:
- Ethnicity:

Questionnaire

1. Have you heard of a medication called clozapine?
    a. Yes – go to Q2
    b. No – read paragraph below to the patient
    c. Don't know – read paragraph below to the patient

Clozapine is an antipsychotic drug. It is used to treat the symptoms of schizophrenia. It helps to reduce things like hearing voices or seeing things that aren't there. It improves concentration and helps to make people's thinking clearer. It has some side effects that are quite common. These include constipation, feeling sleepy, drooling, feeling dizzy when standing up, and a racing heart. We can treat these if they happen. It also has some side effects that are very rare but can be serious. Clozapine can cause the levels of white blood cells to drop. Because of this, before taking clozapine you have to have a blood test. You then need to have your blood tested every week for the first three months. After that it is every two weeks, then once a month. For many people clozapine is the only medicine that works for them.

2. Have you ever asked to take clozapine?
    a. Yes – go to Q3
    b. No – go to Q4
    c. Don't know – go to Q4
    d. Other

3. What happened?

4. If you were offered clozapine now, would you take it?
    a. I'd take it
    b. I wouldn't take it
    c. I might take it
    d. Don't know
    e. Other

5. Why?

6. You would have to have blood taken before starting clozapine. On a scale of 0 to 4, how would you feel about that?

0	1	2	3	4
That **doesn't bother me** at all	I'd be **slightly bothered** but I'd still be willing to try it	I'd be **fairly bothered** but I'd still be willing to try it	I'd be **very bothered** but I'd still be willing to try it	I **wouldn't try clozapine** because of this

Or 5. Don't know

Or 6. Other

7. You would have to have your blood taken regularly whilst taking clozapine. On a scale of 0 to 4, how would you feel about that?

0	1	2	3	4
That **doesn't bother me** at all	I'd be **slightly bothered** but I'd still be willing to try it	I'd be **fairly bothered** but I'd still be willing to try it	I'd be **very bothered** but I'd still be willing to try it	I **wouldn't try clozapine** because of this

Or 5. Don't know

Or 6. Other

8. On a scale of 0 to 4, how much do the side effects of clozapine worry you?

0	1	2	3	4
I'm **not worried** at all	I'm a **bit worried** but I'd still be willing to try it	I'm **fairly worried** but I'd still be willing to try it	I'm **very worried** but I'd still be willing to try it	I **wouldn't try clozapine** because of the side effects

Or 5. Don't know

Or 6. Other

9. Are there any side effects that particularly worry you?

10. In order to start clozapine, sometimes people have to be admitted to hospital for a short time. If that was necessary for you, how would you feel about it?

0	1	2	3	4
That **doesn't bother me** at all	I'd be **slightly bothered** but I'd still be willing to try it	I'd be **fairly bothered** but I'd still be willing to try it	I'd be **very bothered** but I'd still be willing to try it	I **wouldn't try clozapine** because of this

Or 5. Don't know

Or 6. Other

11. If clozapine could be started whilst you were at home, would that make a difference?
    a. Yes
    b. No
    c. Don't know
    d. Other

12. Comparing clozapine to medicines you've had before, how much do you think it would help your symptoms?

0	1	2	3	4
Clozapine would be **a lot less helpful** than other medicines I've had	Clozapine would be **slightly less helpful** than other medicines I've had	Clozapine would be **about the same** as other medicines I've had	Clozapine would be **a bit better** than other medicines I've had	Clozapine would be **a lot better** than other medicines I've had

Or 5. Don't know

Or 6. Other

13. Why?

Appendix F. Patient attitudes to clozapine initiation: free text comments

Table 7-44 Free-text responses to 'why didn't you start the clozapine when it was offered?'

Comment
I devoured it
The voices kept going on. I did take it
I took it a while ago. It was a long time ago. Everything boiled up.
Overheated, slowed down
I didn't want it because of the blood tests, and the changes to the blood cells
I took it
I can't remember
I refused to take it
I'm not sure
I'm not sure

Table 7-45 Free-text responses to follow-up question of 'why' to 'if you were offered clozapine now, would you take it?'

If you were offered clozapine now, would you take it?	Comment
Yes	I have a depot at the moment and it makes me feel deflated and flat
	It is the right thing to do
	If it would help I'd take it. I trust the doctor's opinion - if they say I need it then I'll take it
	I know it would do me good. I trust you
	I take all my medication
	It would be good for my health
	I like my current medicines
	I know what it does
	I want my mental health to recover
	I need something in addition to my current medicines
	It's good to join in and help with taking bloods
	I would speak to the doctor
	I haven't tried it
	Because I've heard of it
No	Because of the side effects
	I'm not sure what the effects might be
	I'm fine at the moment - I don't need it
	There are more negatives than positives. The side effects
	The blood tests
	I only want good food and sleep
	Side effects. I like my current medication
	The constant monitoring. The side effects - salivation, drowsiness. I don't like needles
	I don't have symptoms therefore I don't need it
	I don't want it
	It changes blood cells
	I'm happy with my current medication
	Blood tests
	I don't want to change my medication
	I don't need medicines
	The side effects
	I don't want it
	I don't like tablets

If you were offered clozapine now, would you take it?	Comment
	The dose sounds too high
	I don’t want to have bloods taken
	I'm on too many medicines already
	It kills white blood cells
	I don't know much about it
	Because of the drop in white blood cells
	Because of the side effects
	I don’t know what it will do to me
	I don’t feel ill at the moment
Maybe	Just to try it
	The white cell thing sounds risky
Don’t know	I have epilepsy - only the doctors know about what medicines might affect it
	I wouldn't take it if it wasn't necessary for me
	I'm not sure what it is, or what it does
	Side effects. I like my current medication
	I don’t know how it would affect me
	I don't know anything about it
	Right now I just want to get out of here
	Side effects. Another patient said it's for women
Other	Because I'm in hospital

Table 7-46 Free-text responses to 'which side effects worry you the most?'

Comment
Dizziness - I have a head injury so I already get dizzy
It would make me weaker
Constipation - I already have this
The effect on the WBC, the impact drowsiness would have on my daily life, the racing heart rate
Loss of dignity
The negative effect on my mind. Dizziness, headaches, constipation
Medicines are there to improve and stay positive so I'm not worried about side effects
I haven't taken it so I can't know
I know other people who take clozapine. For them the psychosis is so bad the side effects are worth taking. It's a balance for each individual. Therefore if I needed clozapine I wouldn't care about the side effects because I would need it
All of them. The drooling especially
The strength of the pill makes me worried about collapsing. You can't miss a day of taking clozapine, so you are basically dependent on it
Vomiting, memory loss, drooling. I see other patients that drool, it means you are disabled
Heart palpitations
All of them
Constipation, drowsiness
Reduced sex drive, passing out, any physical effect
Reduced WCC, immune system being destroyed
Weight gain
Reduced white cells
Dizziness and drowsiness - I have these at the moment
It would stop me functioning at school - I have Clopixol injection at the moment and it's stopping me concentrating
Dizziness
Dizziness
Effect on white blood cells, increased heart rate, constipation, sleepiness
Constipation
Not sleeping, worrying, wanting to smoke
The drop in white blood cells
The drop in white blood cells
None in particular, but generally I don't like medicines that make you feel drowsy
Stuttering
Diarrhoea, rushing to the toilet, increased appetite
Fits
Constipation
Drowsiness

Table 7-47 Free-text responses to follow-up question of 'why' to 'on a scale of 0 to 4, how likely do you think clozapine would be to work for you?'

Comment
I've had drooling on amisulpride before, so I wouldn't want this to happen again. I don't need clozapine. But I recognise that if psychosis is really bad then people need clozapine and then for them any negative problems (having to have bloods done, the side effects, being admitted) are outweighed by the benefits. So the problem is people not having any insight into the severity of their psychosis
I haven't taken it so I can't really know
The side effects. I think clozapine would help but the side effects mean I'd prefer my current treatment
I don't like changing medicines
I don't know until I've tried it
I'm not sure
I only want injections - I'm old fashioned
Risperidone works for me
I don't know much about it. But if it's better than other medicines I'd take it despite the side effects and the bloods
I don't have hallucinations. I don't know why I'd need to take it
I'm homeless, so would have to come into hospital for clozapine so I wouldn't want to do that
I want aripiprazole depot. I only want to take the advice of the doctors on medication choice
Side effects
The side effects. I already have constipation so that's worrying
I have never tried clozapine so how would I know?
It has certain vital elements that other medicines don't have
I'm not sure what the effect of clozapine would be. I don't like taking medicines
From what I've heard from other patients, and also research I've done on the internet
My current medicines are no good for me
The side effects are similar to my current medicine
Constipation
I don't believe in any medicines
It attacks the immune system
The side effects - the reduced WCC means you might get viral infections
The side effects. Then you have to take more medicines for the side effects
I don't know
My body isn't used to it
It would keep me out of hospital
I would be worried about starting clozapine at home because side effects wouldn't be monitored
Starting at home wouldn't make a difference because I'm on too many tablets already. Clozapine would much less helpful because it's a new drug to me
I've never taken it; how would I know?
It would have a sweet taste
I trust what you say. If you think I need clozapine, I'll take it
It would give me more motivation
I haven't tried clozapine. But quetiapine has no side effects so I prefer that
Because of the side effects
The side effects, and if you need to be admitted to hospital
Because of the benefits of clozapine

Comment
I'm not sure
I haven't taken clozapine so I don't know if it would be better than other medicines
That's what it's designed to do
We need to share the blood that we have
I've never taken it so wouldn't know
I haven't tried it
Because it would help

Appendix G. Statistical data for chapter 5

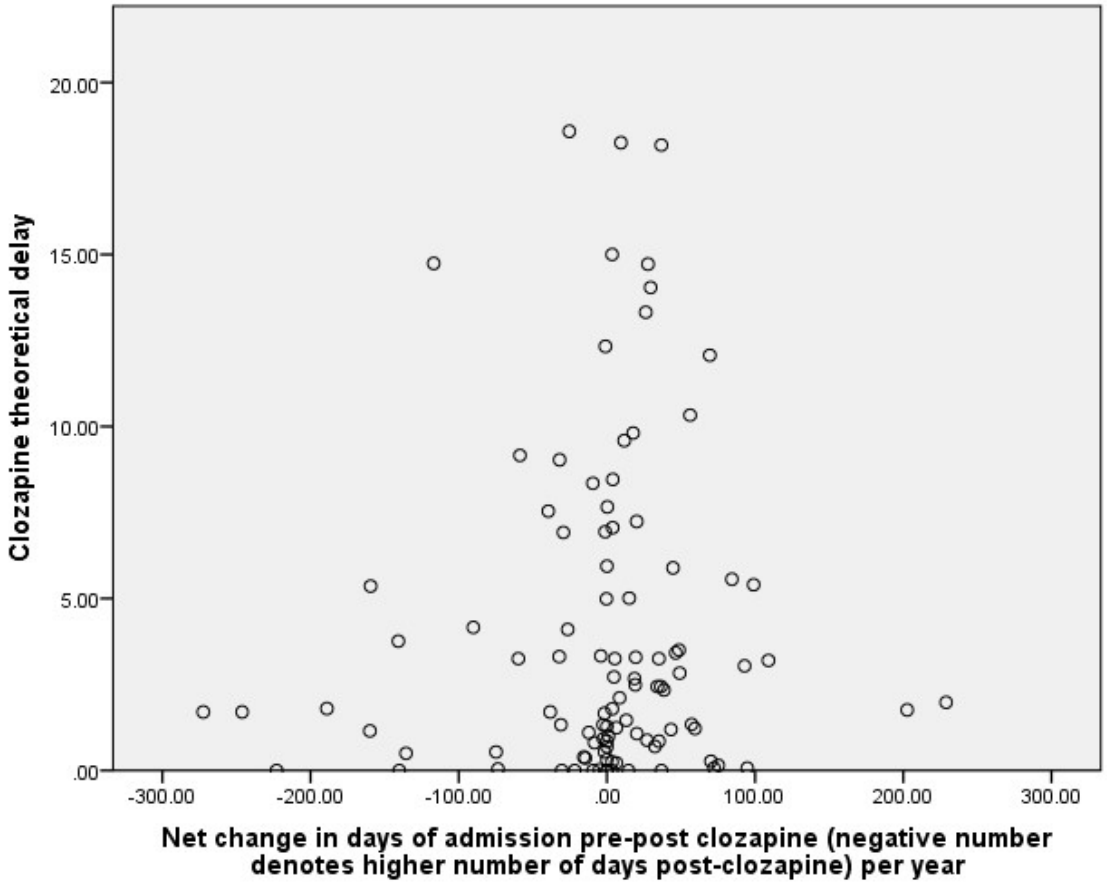


Figure 7-3 Scatter plot, intent to treat group, analysis method 1

Table 7-48 Z-score for net change in days of admission post-clozapine, Intent to treat group, analysis method 1

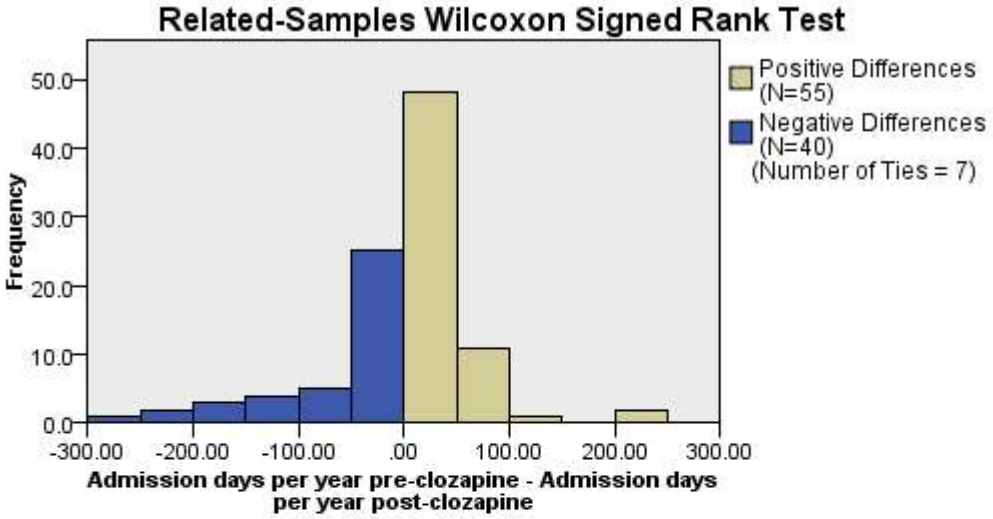
	Frequency	Percent	Valid Percent	Cumulative Percent
Extreme Outliers	1	1.0	1.0	1.0
Probable Outliers	4	3.9	3.9	4.9
Potential Outliers	3	2.9	2.9	7.8
Normal range	94	92.2	92.2	100.0
Total	102	100.0	100.0	

Table 7-49 Skewness and kurtosis for outcome data, Intent to treat group, analysis method 1

	Net change in number of admissions per year	Net change in days of admission per year	Clozapine theoretical delay	Total number of antipsychotic prescriptions before clozapine
N	102	102	102	102
Mean	0.7347	-2.9848	3.9275	5.45
Median	0.4300	3.4950	2.0450	4.00
Std. Deviation	1.19069	75.53929	4.61050	3.952
Variance	1.418	5706.184	21.257	15.616
Skewness	3.198	-0.937	1.582	2.083
Std. Error of Skewness	0.239	0.239	0.239	0.239
Kurtosis	15.403	3.439	1.855	5.526
Std. Error of Kurtosis	0.474	0.474	0.474	0.474
Range	9.37	501.30	18.58	23
z-skewness	13.38	-3.92	6.62	8.72
z-kurtosis	32.50	7.26	3.91	11.66

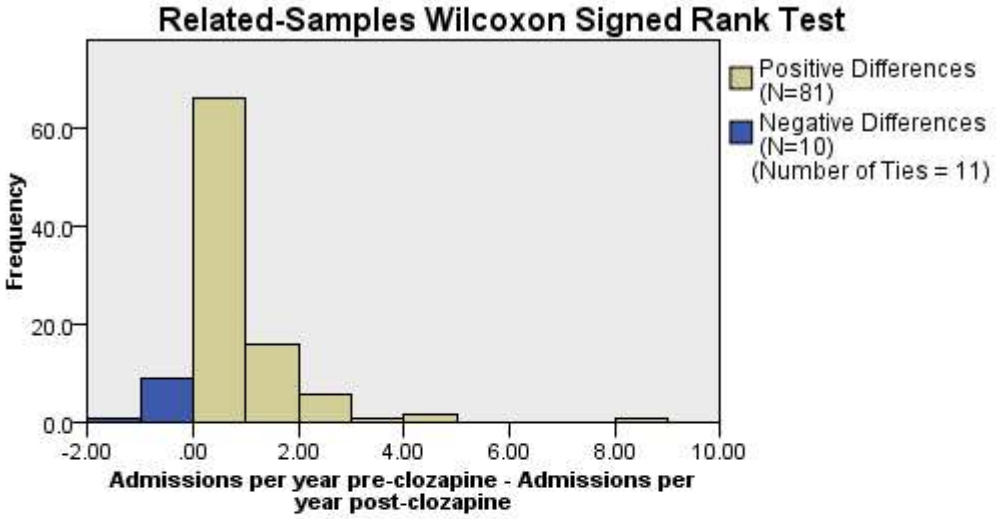
Table 7-50 Kolmogorov-Smirnov and Shapiro-Wilk tests of normality, intent to treat group, method 1

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Net change in days of admission per year	0.191	102	<0.0005	0.871	102	<0.0005
Net change in number of admissions per year	0.200	102	<0.0005	0.720	102	<0.0005
Total number of antipsychotic prescriptions before clozapine	0.222	102	<0.0005	0.794	102	<0.0005
Clozapine theoretical delay	0.213	102	<0.0005	0.791	102	<0.0005



Total N	102
Test Statistic	2,574.500
Standard Error	269.407
Standardized Test Statistic	1.093
Asymptotic Sig. (2-sided test)	.274

Figure 7-4 Wilcoxon signed rank test, change in days of admission per year, analysis method 1



Total N	102
Test Statistic	3,841.000
Standard Error	252.652
Standardized Test Statistic	6.919
Asymptotic Sig. (2-sided test)	.000

Figure 7-5 Wilcoxon signed rank test, change in admissions per year, analysis method 1

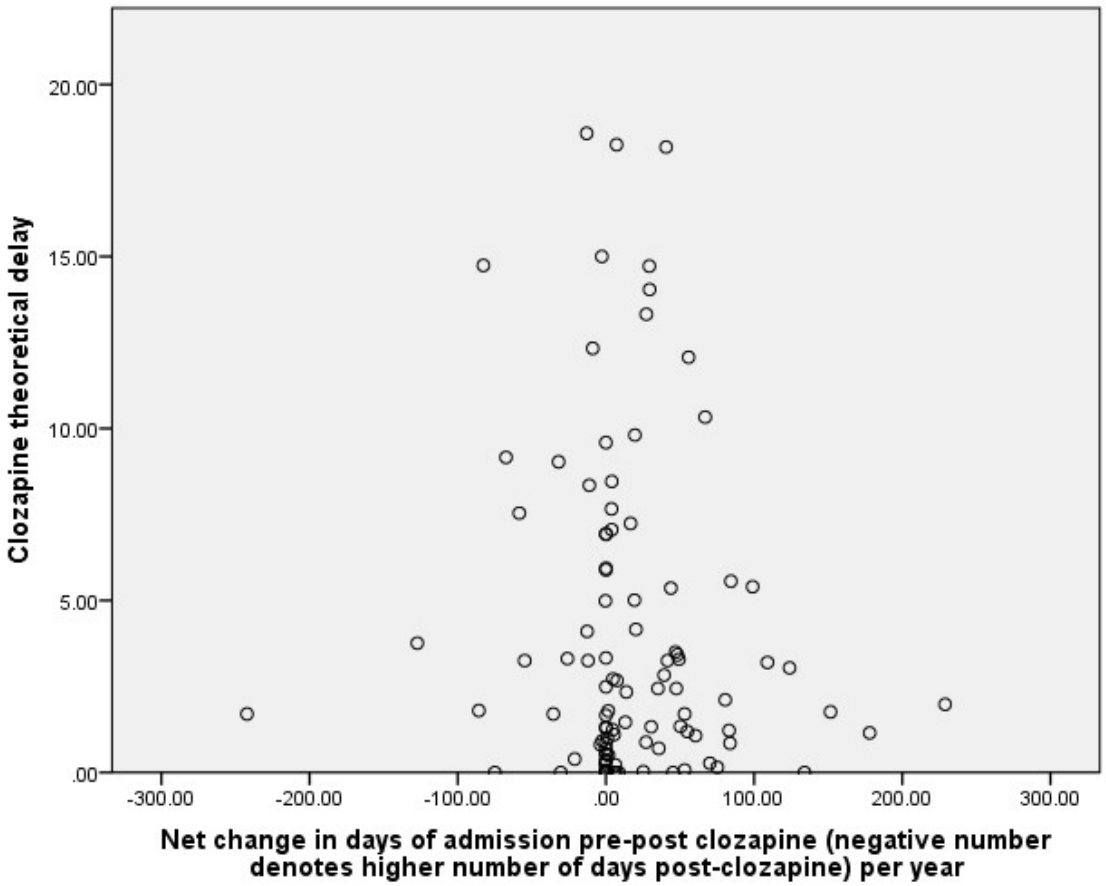


Figure 7-6 Scatterplot, intent to treat group, analysis method 2

Table 7-51 Z-score for net change in days of admission post-clozapine, Intent to treat group, analysis method 2

	Frequency	Percent	Valid Percent	Cumulative Percent
Extreme outliers	1	1.0	1.0	1.0
Probable outliers	1	1.0	1.0	2.0
Potential outliers	2	2.0	2.0	3.9
Normal range	98	96.1	96.1	100.0
Total	102	100.0	100.0	

Table 7-52 Paired samples t-test, intent to treat group, method 2

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Change in days of admission per year	16.73735	57.35719	5.67921	5.47133	28.00337	2.947	101	0.004
Change in admissions per year	0.34265	0.64808	0.06417	0.21535	0.46994	5.340	101	<0.0005

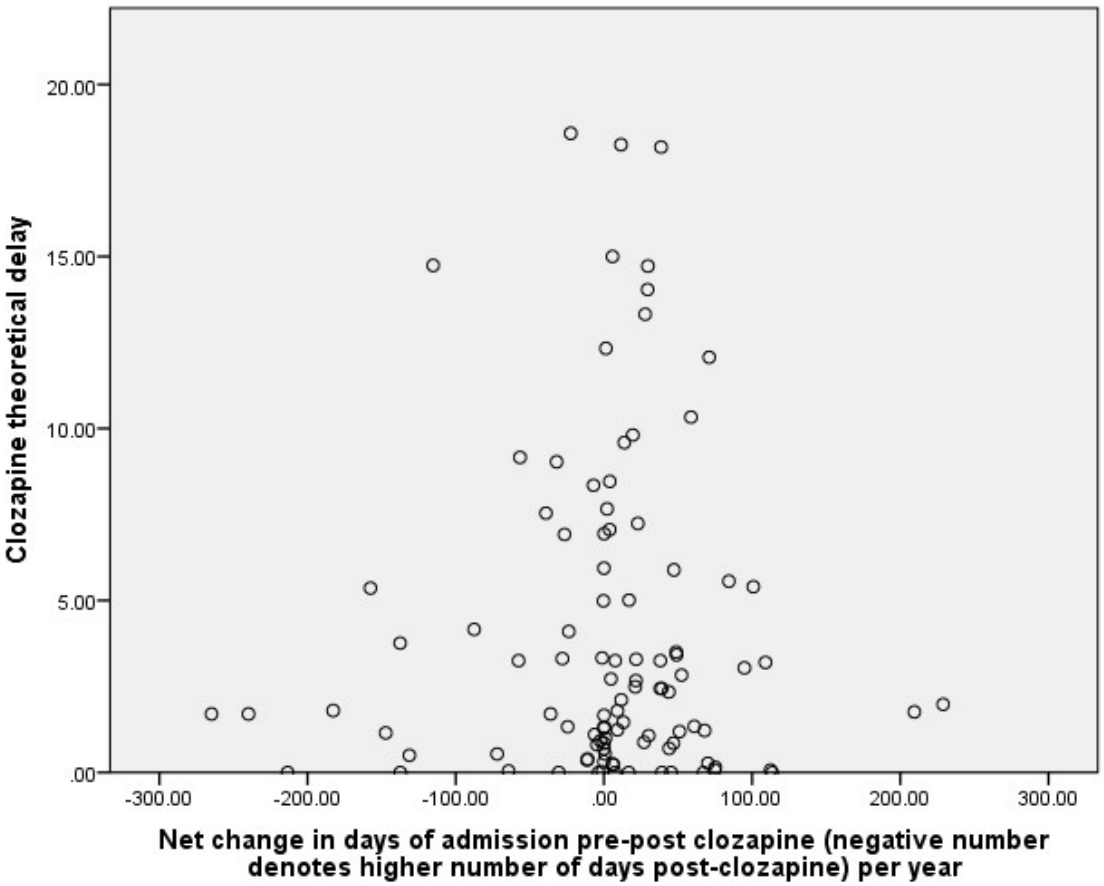


Figure 7-7 Scatter plot, intent to treat group, analysis method 3

Table 7-53 Z-score for net change in days of admission post-clozapine, Intent to treat group, analysis method 3

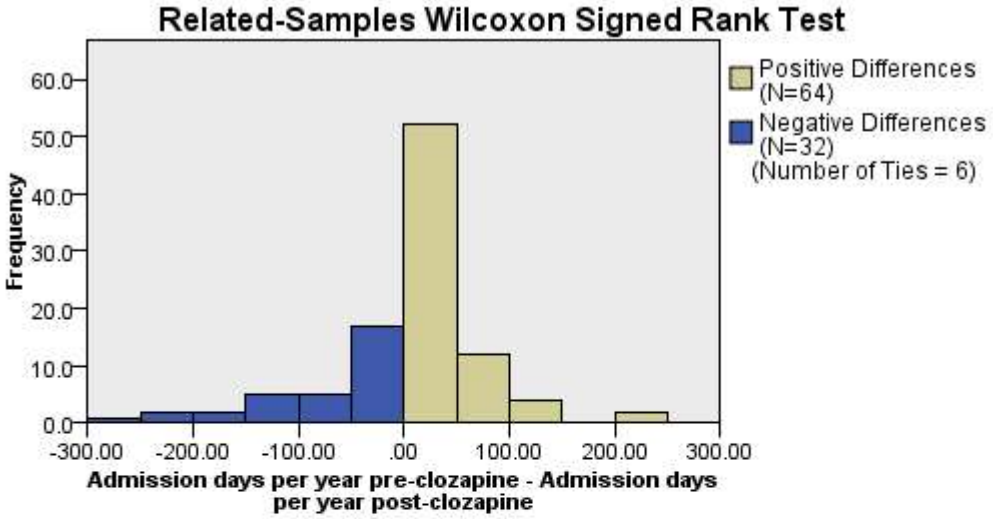
	Frequency	Percent	Valid Percent	Cumulative Percent
Extreme Outliers	1	1.0	1.0	1.0
Probable Outliers	4	3.9	3.9	4.9
Potential Outliers	3	2.9	2.9	7.8
Normal range	94	92.2	92.2	100.0
Total	102	100.0	100.0	

Table 7-54 Skewness and kurtosis for analysis method 3

	Clozapine theoretical delay	Net change in days of admission per year	Net change in number of admissions per year	Total number of antipsychotic prescriptions before clozapine
N	102	102	102	102
Mean	3.9275	2.4234	0.7347	5.45
Std. Error of Mean	0.45651	7.54320	0.11790	0.391
Median	2.0450	6.0850	0.4300	4.00
Std. Deviation	4.61050	76.18259	1.19069	3.952
Variance	21.257	5803.787	1.418	15.616
Skewness	1.582	-0.882	3.198	2.083
Std. Error of Skewness	0.239	0.239	0.239	0.239
Kurtosis	1.855	3.084	15.403	5.526
Std. Error of Kurtosis	0.474	0.474	0.474	0.474
z-skewness z-kurtosis	6.62 3.91	-3.69 6.51	13.38 32.50	8.72 11.66

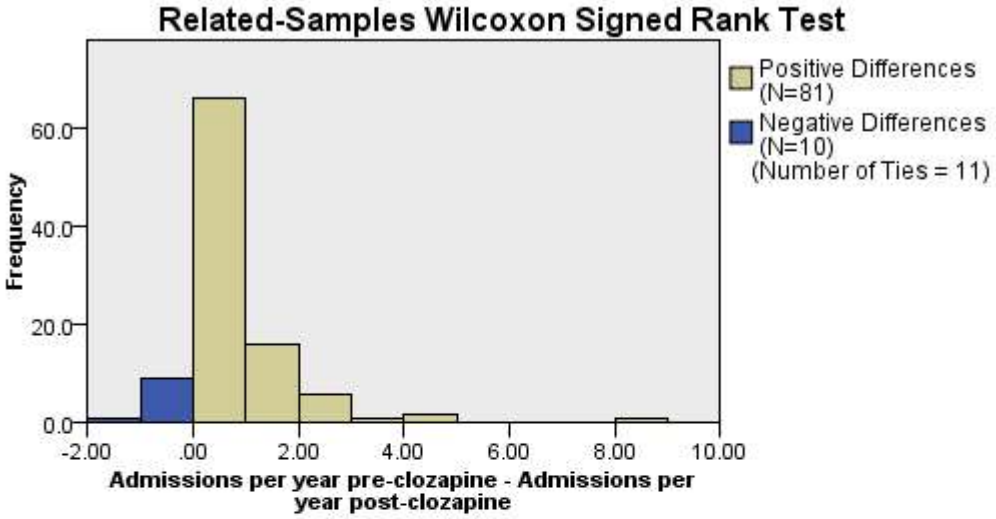
Table 7-55 Kolmogorov-Smirnov and Shapiro-Wilk tests of normality, intent to treat group, method 3

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Net change in days of admission per year	0.194	102	<0.0005	0.886	102	<0.0005
Net change in number of admissions per year	0.200	102	<0.0005	0.720	102	<0.0005
Total number of antipsychotic prescriptions before clozapine	0.222	102	<0.0005	0.794	102	<0.0005
Clozapine theoretical delay	0.213	102	<0.0005	0.791	102	<0.0005



Total N	102
Test Statistic	2,879.500
Standard Error	273.649
Standardized Test Statistic	2.015
Asymptotic Sig. (2-sided test)	.044

Figure 7-8 Wilcoxon signed rank test, change in days of admission per year, analysis method 3



Total N	102
Test Statistic	3,841.000
Standard Error	252.652
Standardized Test Statistic	6.919
Asymptotic Sig. (2-sided test)	.000

Figure 7-9 Wilcoxon signed rank test, change in admissions per year, analysis method 3

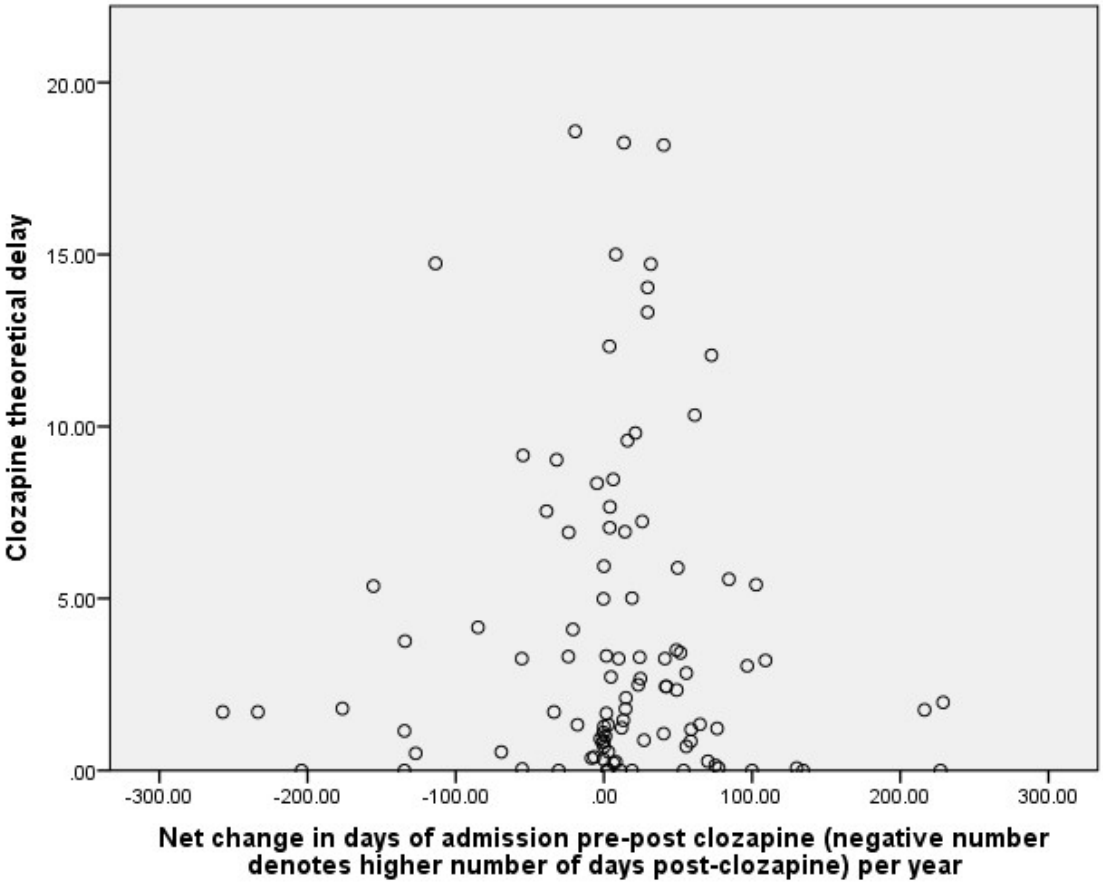


Figure 7-10 Scatter plot, intent to treat group, analysis method 4

Table 7-56 Z-score for net change in days of admission post-clozapine, Intent to treat group, analysis method 4

	Frequency	Percent	Valid Percent	Cumulative Percent
Probable outliers	3	2.9	2.9	2.9
Normal range	99	97.1	97.1	100.0
Total	102	100.0	100.0	

Table 7-57 Paired samples t-test, intent to treat group, method 4

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Change in days of admission per year	7.97725	79.37166	7.85897	-7.61282	23.56733	1.015	101	0.313
Change in admissions per year	0.73529	1.19063	0.11789	0.50143	0.96916	6.237	101	<0.0005

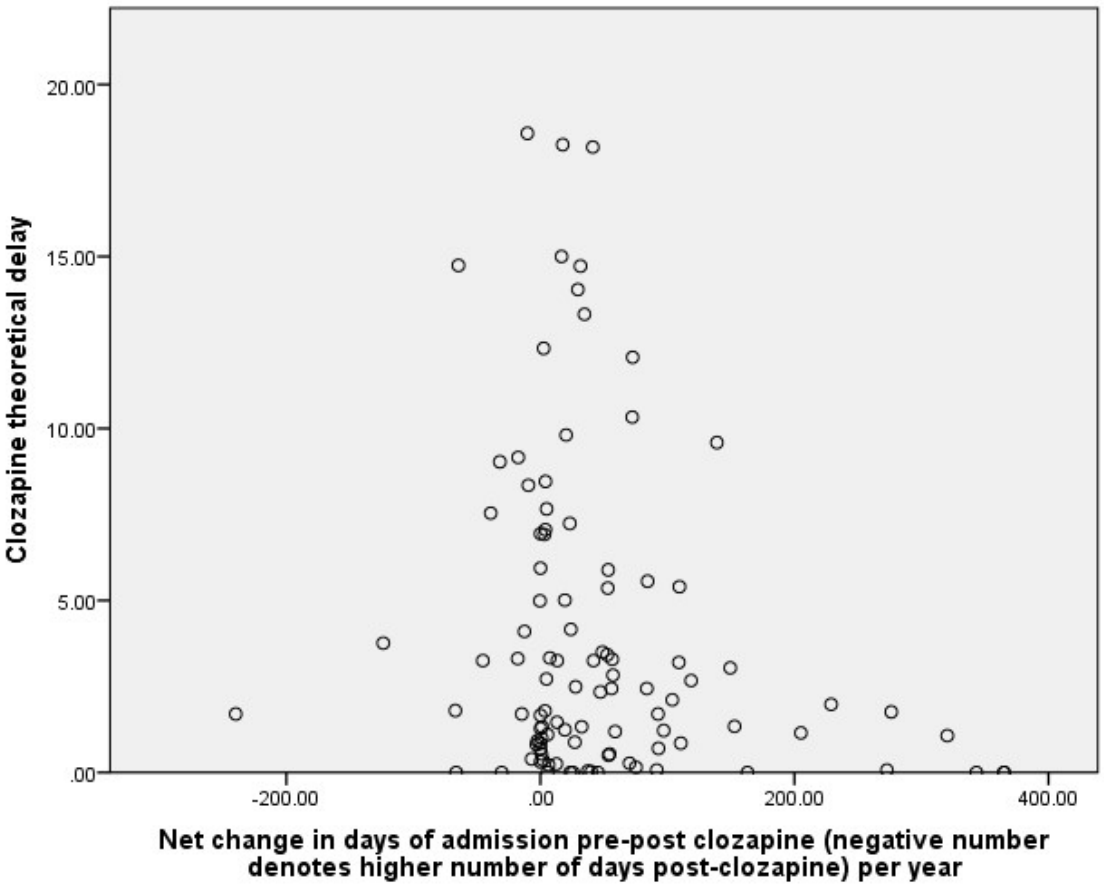


Figure 7-11 Scatter plot, intent to treat group, analysis method 5

Table 7-58 Z-score for net change in days of admission post-clozapine, Intent to treat group, analysis method 5

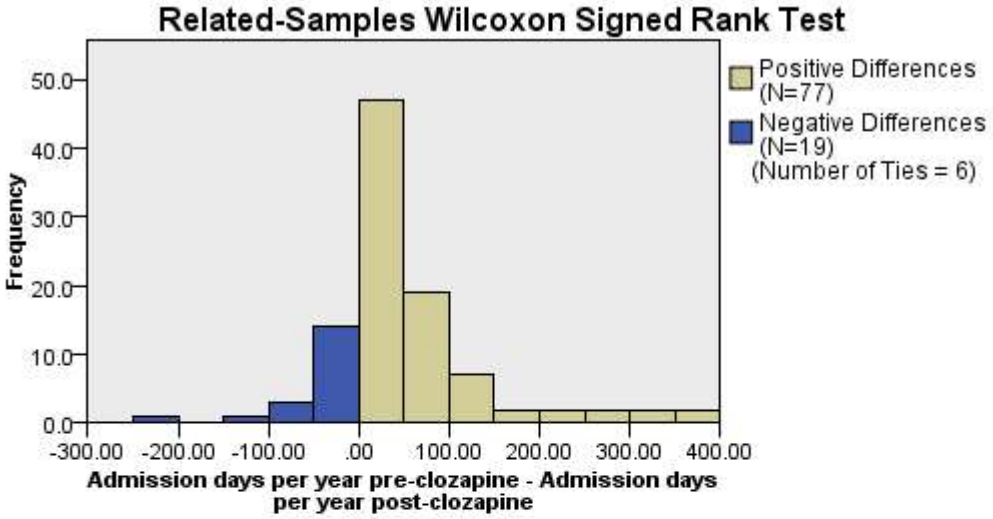
	Frequency	Percent	Valid Percent	Cumulative Percent
Extreme outliers	2	2.0	2.0	2.0
Probable outliers	3	2.9	2.9	5.9
Potential outliers	2	2.0	2.0	7.8
Normal range	94	92.2	92.2	100.0
Total	102	100.0	100.0	

Table 7-59 Skewness and kurtosis for analysis method 5

	Net change in days of admission per year	Net change in number of admissions per year	Clozapine theoretical delay	Total number of antipsychotic prescriptions before clozapine
N	102	102	102	102
Mean	47.3139	0.7347	3.9275	5.45
Std. Error of Mean	9.18974	0.11790	0.45651	0.391
Median	23.7350	0.4300	2.0450	4.00
Std. Deviation	92.81178	1.19069	4.61050	3.952
Variance	8614.027	1.418	21.257	15.616
Skewness	1.396	3.198	1.582	2.083
Std. Error of Skewness	0.239	0.239	0.239	0.239
Kurtosis	3.960	15.403	1.855	5.526
Std. Error of Kurtosis z-skewness z-kurtosis	0.474 5.84 8.35	0.474 13.38 32.50	0.474 6.62 3.91	0.474 8.72 11.66

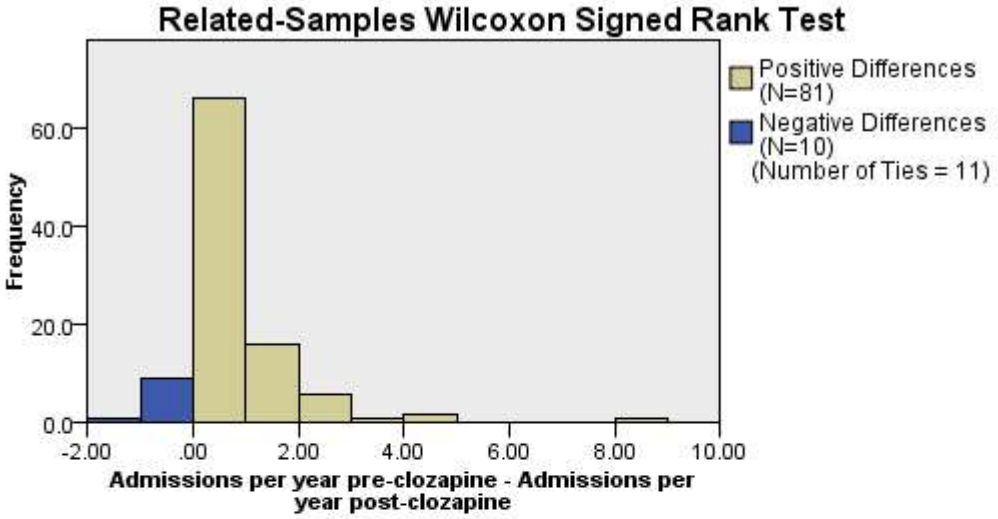
Table 7-60 Kolmogorov-Smirnov and Shapiro-Wilk tests of normality, intent to treat group, method 5

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Net change in days of admission pre-post clozapine per year	0.186	102	<0.0005	0.829	102	<0.0005
Net change in number of admissions per year	0.200	102	<0.0005	0.720	102	<0.0005
Total number of antipsychotic prescriptions before clozapine	0.222	102	<0.0005	0.794	102	<0.0005
Clozapine theoretical delay	0.213	102	<0.0005	0.791	102	<0.0005



Total N	102
Test Statistic	3,908.000
Standard Error	273.649
Standardized Test Statistic	5.774
Asymptotic Sig. (2-sided test)	.000

Figure 7-12 Wilcoxon signed rank test, change in days of admission per year, analysis method 5



Total N	102
Test Statistic	3,841.000
Standard Error	252.652
Standardized Test Statistic	6.919
Asymptotic Sig. (2-sided test)	.000

Figure 7-13 Wilcoxon signed rank test, change in admissions per year, analysis method 5

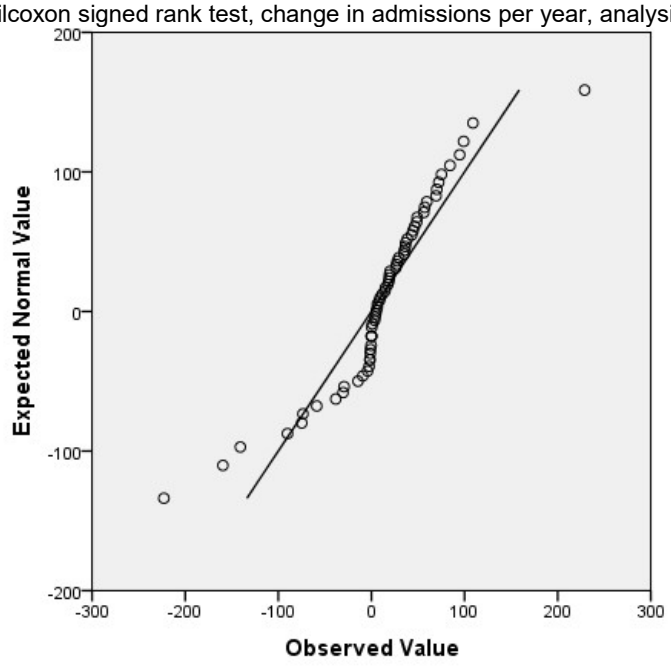
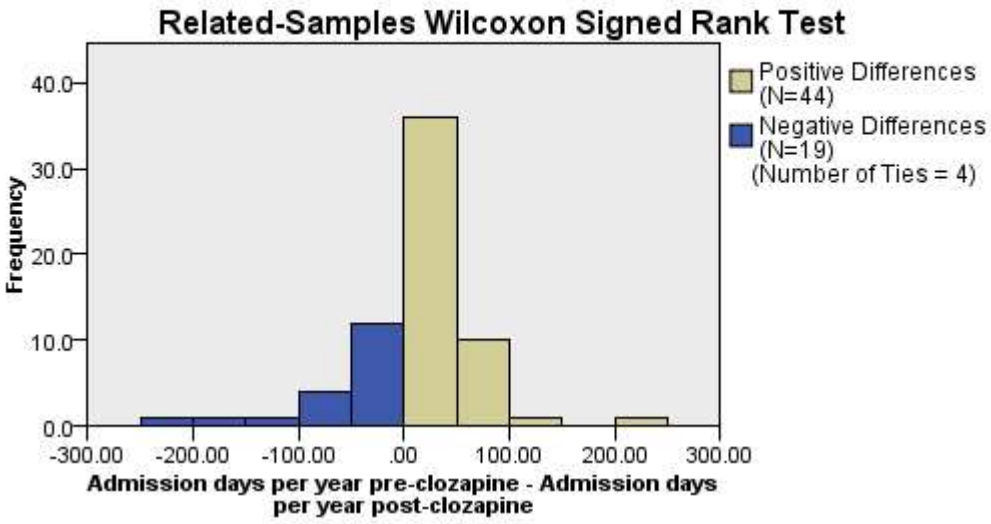


Figure 7-14 Q-Q plot, net change in days of admission per year, analysis method 1, clozapine continuers

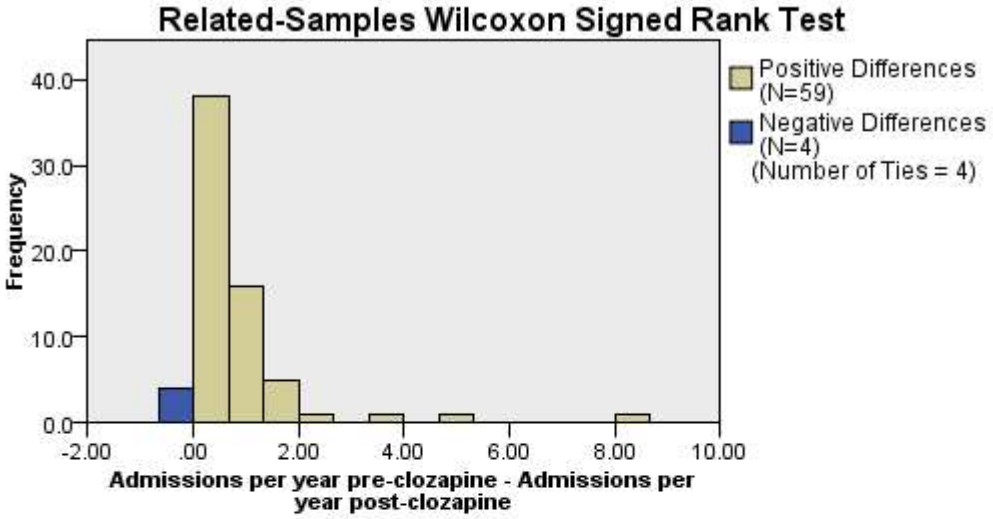
Table 7-61 Paired samples t-test, clozapine continuers group, method 1

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Change in admission days per year	12.39896	62.12410	7.58967	-2.75430	27.55221	1.634	66	0.107
Change in admissions per year	0.77313	1.21173	0.14804	0.47757	1.06870	5.223	66	<0.0005



Total N	67
Test Statistic	1,443.000
Standard Error	146.068
Standardized Test Statistic	2.978
Asymptotic Sig. (2-sided test)	.003

Figure 7-15 Wilcoxon signed rank test, change in days of admission per year, clozapine continuers, analysis method 1



Total N	67
Test Statistic	1,944.000
Standard Error	146.062
Standardized Test Statistic	6.408
Asymptotic Sig. (2-sided test)	.000

Figure 7-16 Wilcoxon signed rank test, change in admissions per year, clozapine continuers, analysis method 1

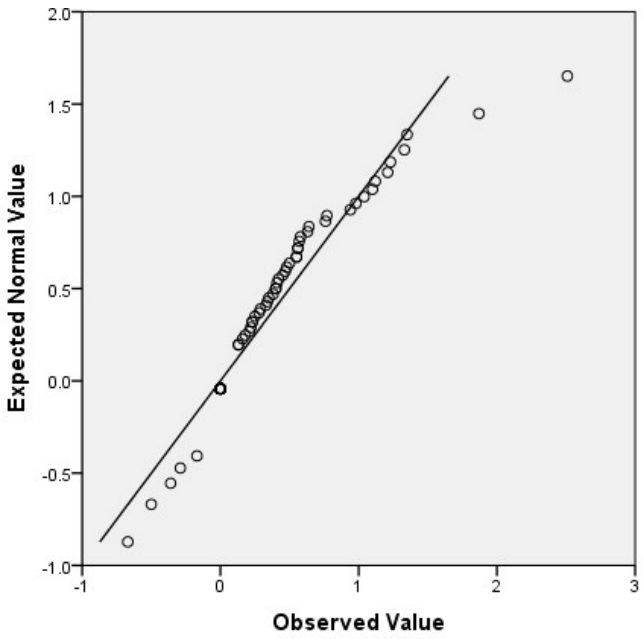
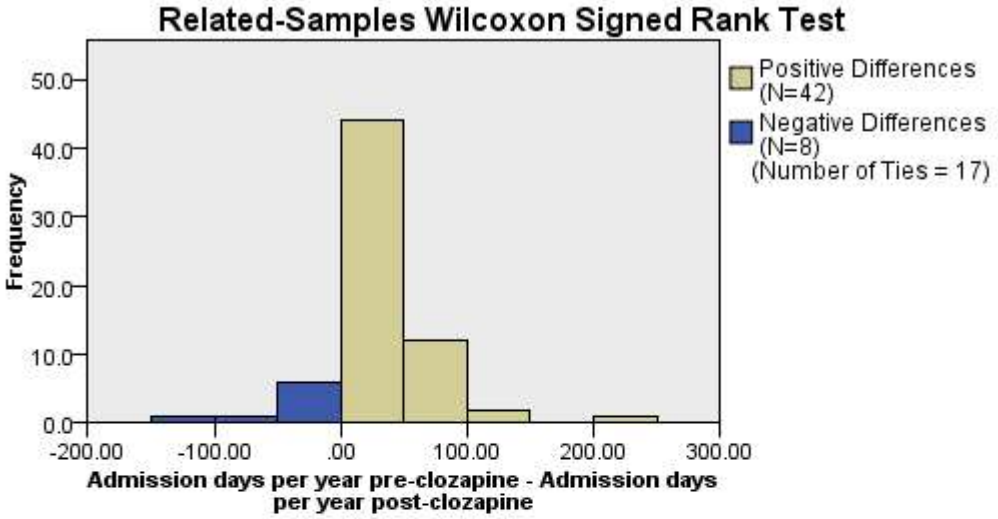


Figure 7-17 Q-Q plot, net change in days of admission per year, analysis method 2, clozapine continuers

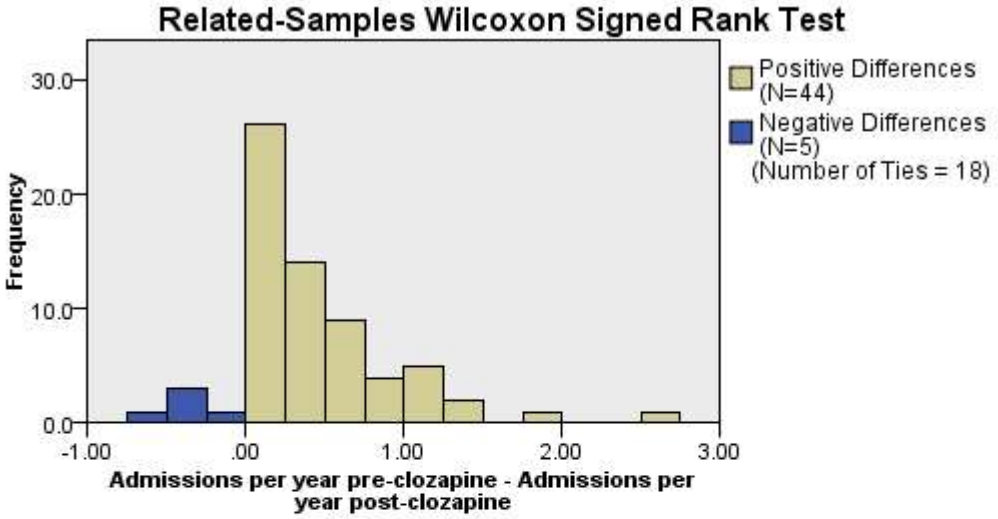
Table 7-62 Paired samples t-test, clozapine continuers group, method 2

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Change in days of admission per year	24.73731	47.58048	5.81288	13.13152	36.34311	4.256	66	<0.0005
Change in admissions per year	0.38940	0.53612	0.06550	0.25863	0.52017	5.945	66	<0.0005



Total N	67
Test Statistic	1,109.000
Standard Error	103.592
Standardized Test Statistic	4.552
Asymptotic Sig. (2-sided test)	.000

Figure 7-18 Wilcoxon signed rank test, change in days of admission per year, clozapine continuers, analysis method 2



Total N	67
Test Statistic	1,129.000
Standard Error	100.525
Standardized Test Statistic	5.138
Asymptotic Sig. (2-sided test)	.000

Figure 7-19 Wilcoxon signed rank test, change in admissions per year, clozapine continuers, analysis method 2

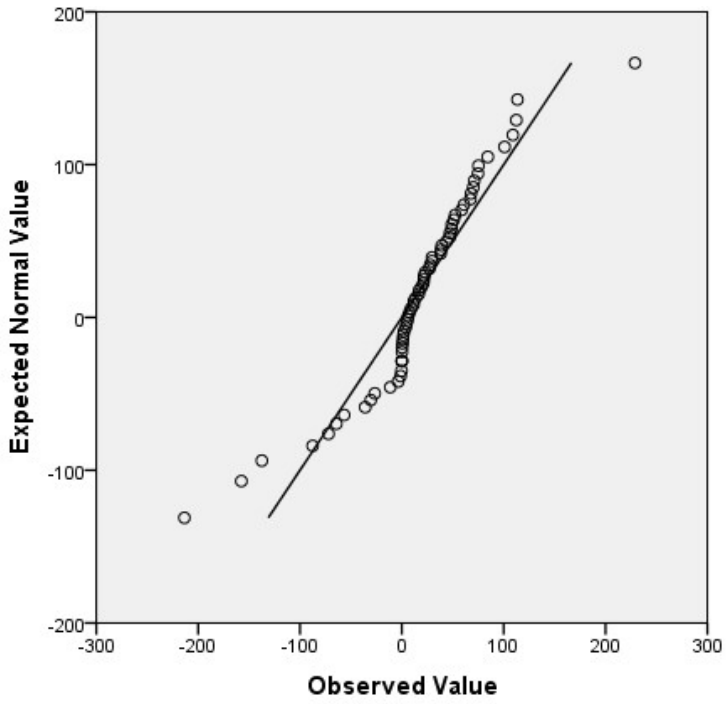
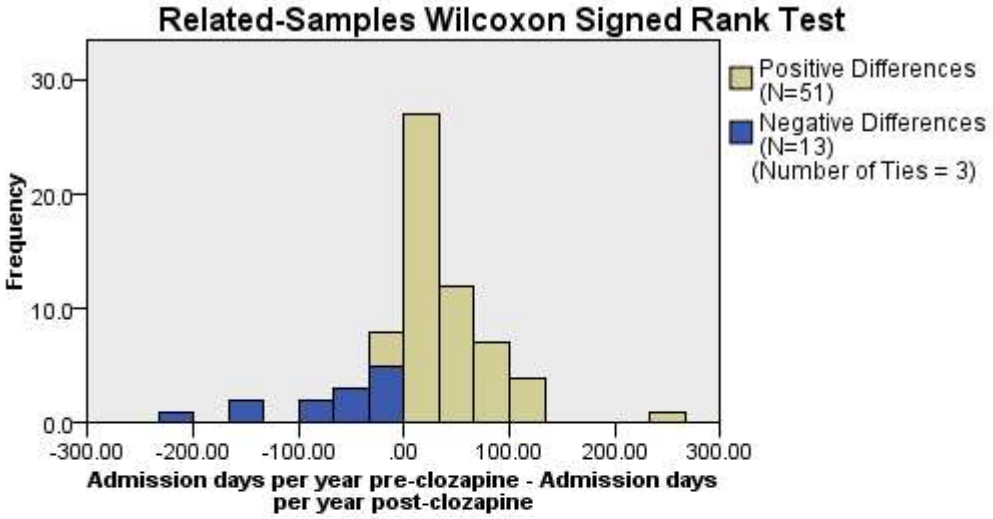


Figure 7-20 Q-Q plot, net change in days of admission per year, analysis method 3, clozapine continuers

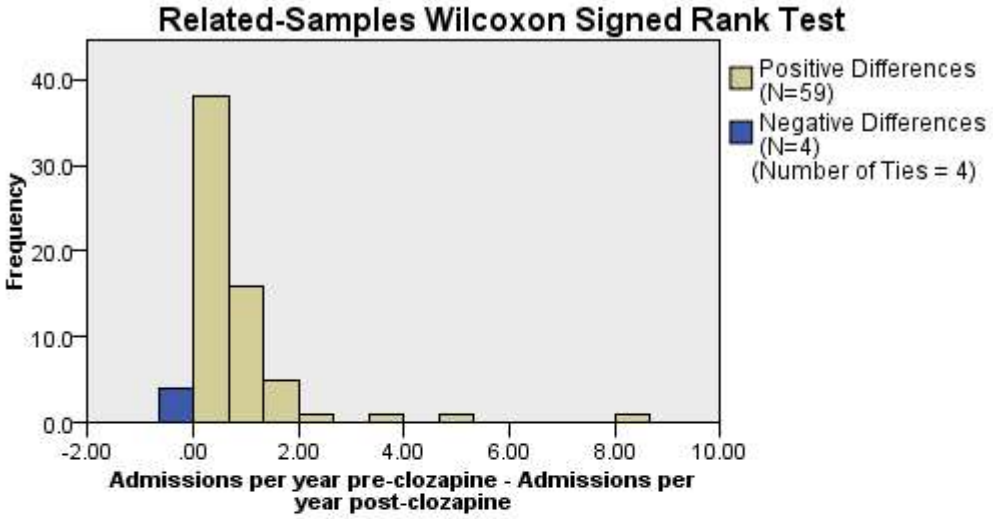
Table 7-63 Paired samples t-test, clozapine continuers group, method 3

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Change in days of admission per year	17.69836	63.24476	7.72658	2.27175	33.12497	2.291	66	0.025
Change in admissions per year	0.77313	1.21173	0.14804	0.47757	1.06870	5.223	66	<0.0005



Total N	67
Test Statistic	1,577.000
Standard Error	149.533
Standardized Test Statistic	3.591
Asymptotic Sig. (2-sided test)	.000

Figure 7-21 Wilcoxon signed rank test, change in days of admission per year, clozapine continuers, analysis method 3



Total N	67
Test Statistic	1,944.000
Standard Error	146.062
Standardized Test Statistic	6.408
Asymptotic Sig. (2-sided test)	.000

Figure 7-22 Wilcoxon signed rank test, change in admissions per year, clozapine continuers, analysis method 3

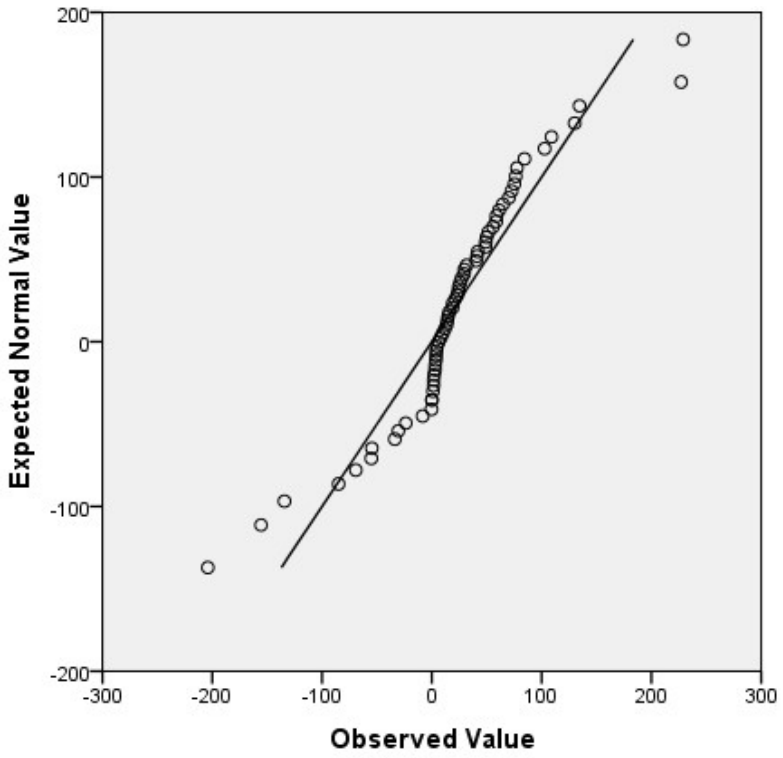
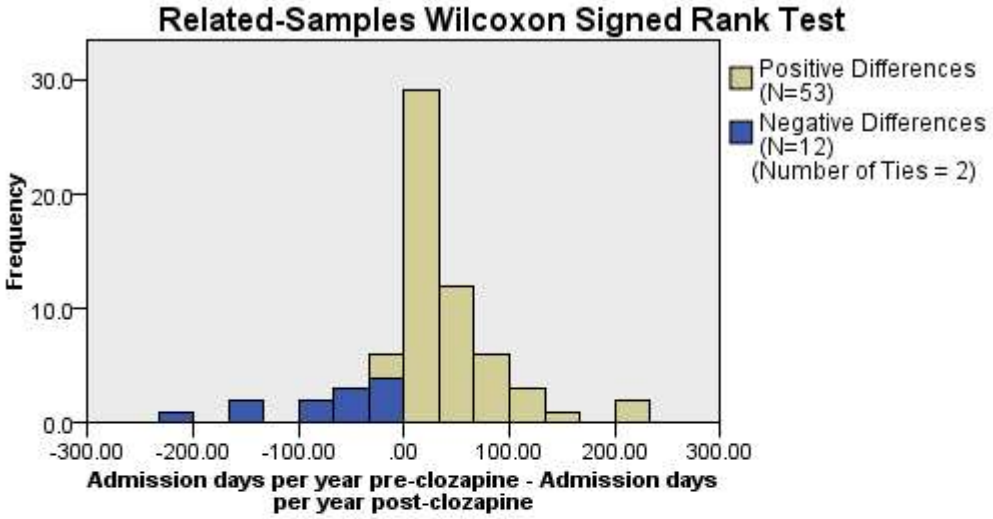


Figure 7-23 Q-Q plot, net change in days of admission per year, analysis method 4, clozapine continuers

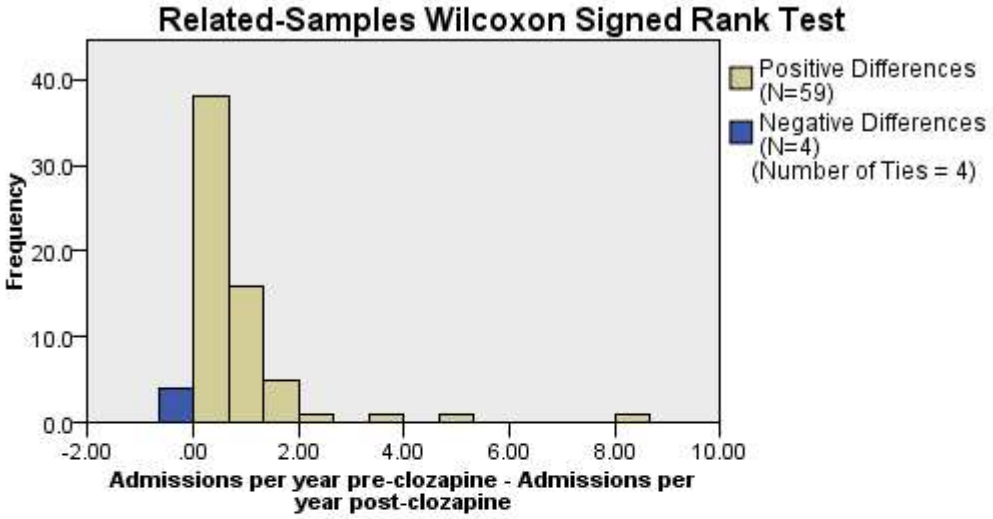
Table 7-64 Paired samples t-test, clozapine continuers group, method 4

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Change in days of admission per year	23.18761	68.09948	8.31968	6.57684	39.79838	2.787	66	0.007
Change in admissions per year	0.77313	1.21173	0.14804	0.47757	1.06870	5.223	66	<0.0005



Total N	67
Test Statistic	1,664.000
Standard Error	153.024
Standardized Test Statistic	3.865
Asymptotic Sig. (2-sided test)	.000

Figure 7-24 Wilcoxon signed rank test, change in days of admission per year, clozapine continuers, analysis method 4



Total N	67
Test Statistic	1,944.000
Standard Error	146.062
Standardized Test Statistic	6.408
Asymptotic Sig. (2-sided test)	.000

Figure 7-25 Wilcoxon signed rank test, change in admissions per year, clozapine continuers, analysis method 4

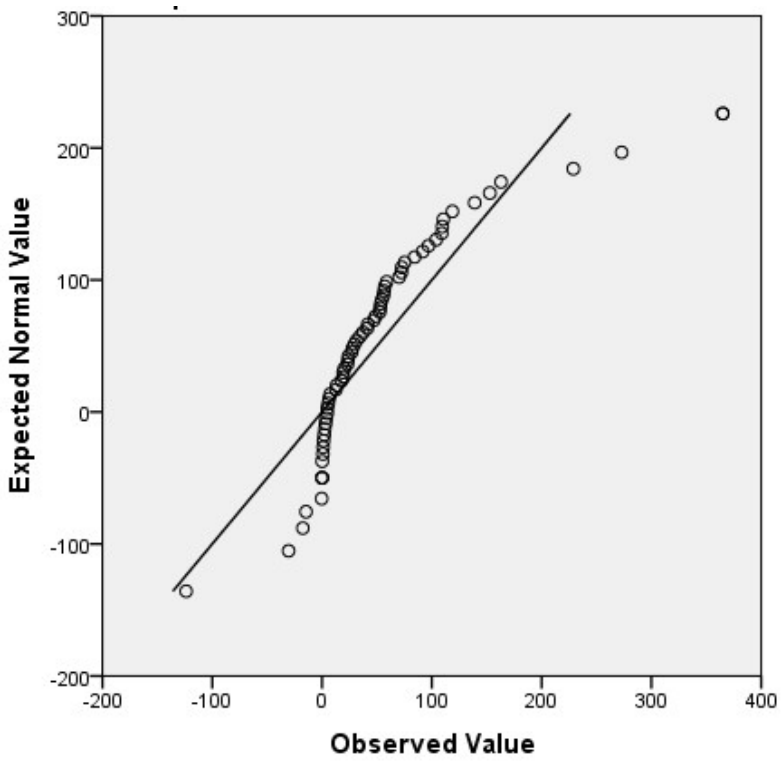
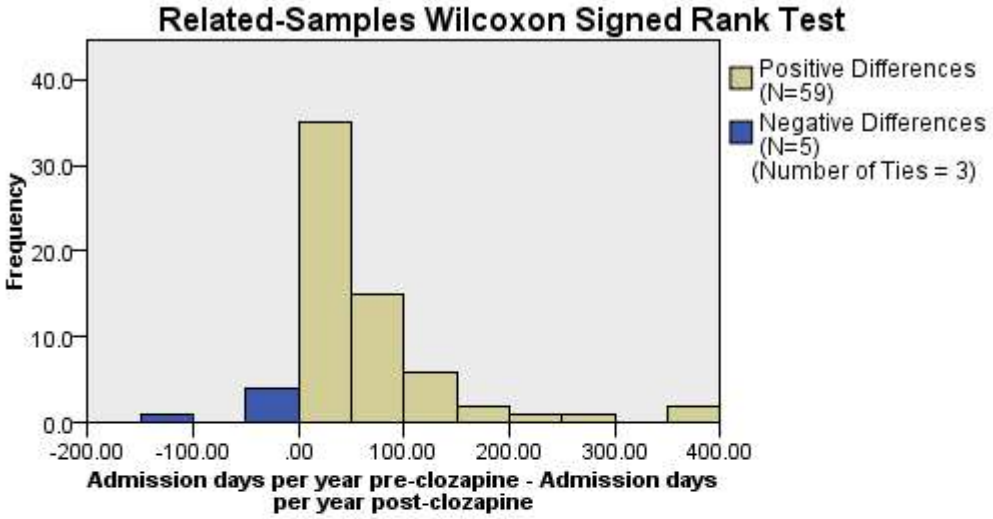


Figure 7-26 Q-Q plot, net change in days of admission per year, analysis method 5, clozapine continuers

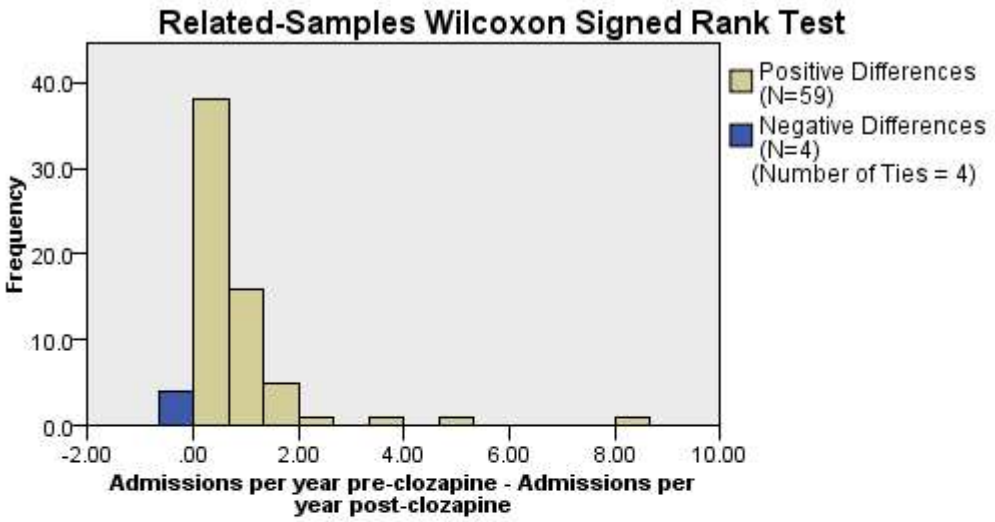
Table 7-65 Paired samples t-test, clozapine continuers group, method 5

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Change in days of admission per year	54.32075	80.77452	9.86818	34.61829	74.02320	5.505	66	<0.0005
Change in admissions per year	0.77313	1.21173	0.14804	0.47757	1.06870	5.223	66	<0.0005



Total N	67
Test Statistic	1,957.000
Standard Error	149.532
Standardized Test Statistic	6.132
Asymptotic Sig. (2-sided test)	.000

Figure 7-27 Wilcoxon signed rank test, change in days of admission per year, clozapine continuers, analysis method 5



Total N	67
Test Statistic	1,944.000
Standard Error	146.062
Standardized Test Statistic	6.408
Asymptotic Sig. (2-sided test)	.000

Figure 7-28 Wilcoxon signed rank test, change in admissions per year, clozapine continuers, analysis method 5

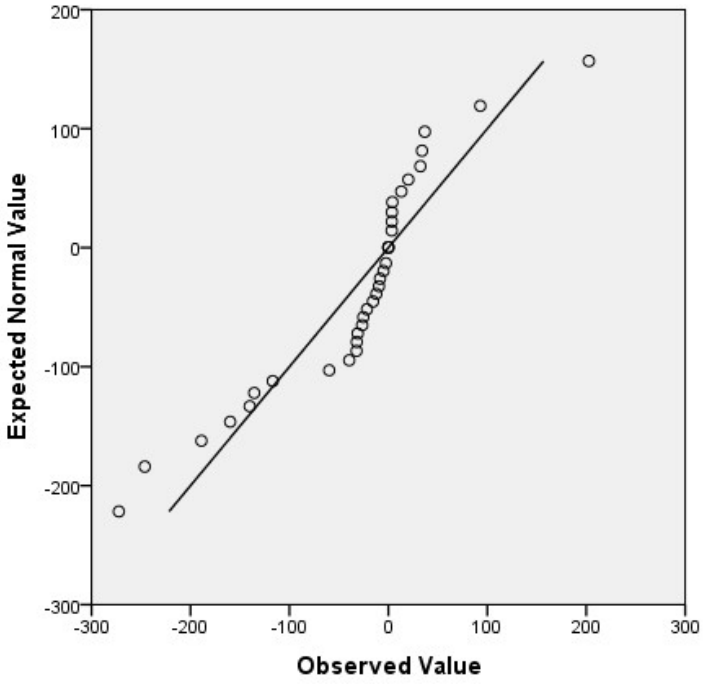
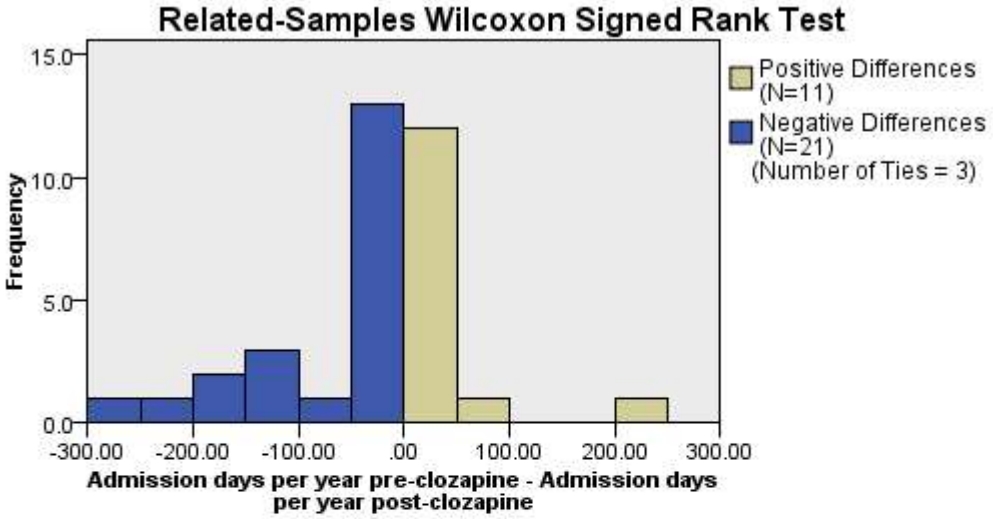


Figure 7-29 Q-Q plot, net change in days of admission per year, analysis method 1, clozapine discontinuers

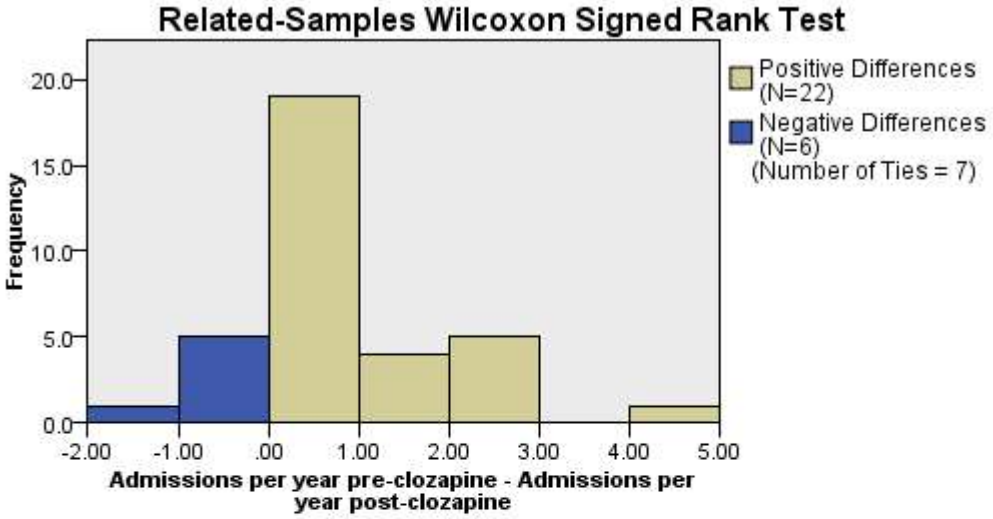
Table 7-66 Paired samples t-test, clozapine discontinuers group, method 1

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Change in days of admissions per year	-32.43400	89.99902	15.21261	-63.3497	-1.51826	-2.132	34	0.040
Change in admissions per year	0.66286	1.16305	0.19659	0.26334	1.06238	3.372	34	0.002



Total N	35
Test Statistic	150.000
Standard Error	53.479
Standardized Test Statistic	-2.132
Asymptotic Sig. (2-sided test)	.033

Figure 7-30 Wilcoxon signed rank test, change in days of admission per year, clozapine discontinuers, analysis method 1



Total N	35
Test Statistic	337.500
Standard Error	43.912
Standardized Test Statistic	3.063
Asymptotic Sig. (2-sided test)	.002

Figure 7-31 Wilcoxon signed rank test, change in admissions per year, clozapine discontinuers, analysis method 1

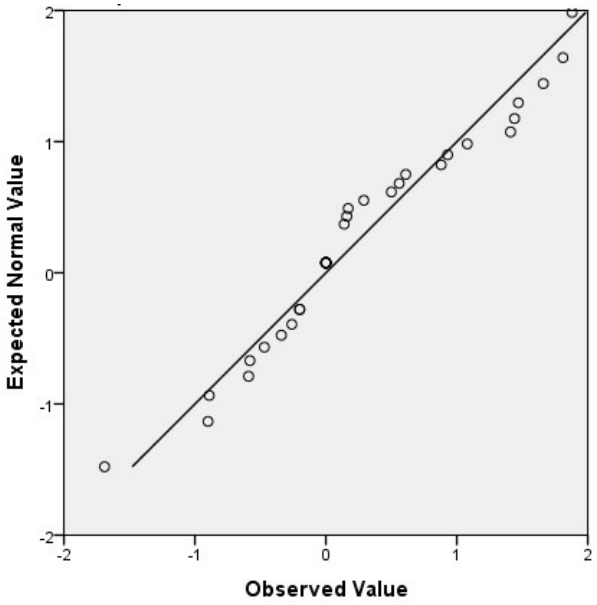
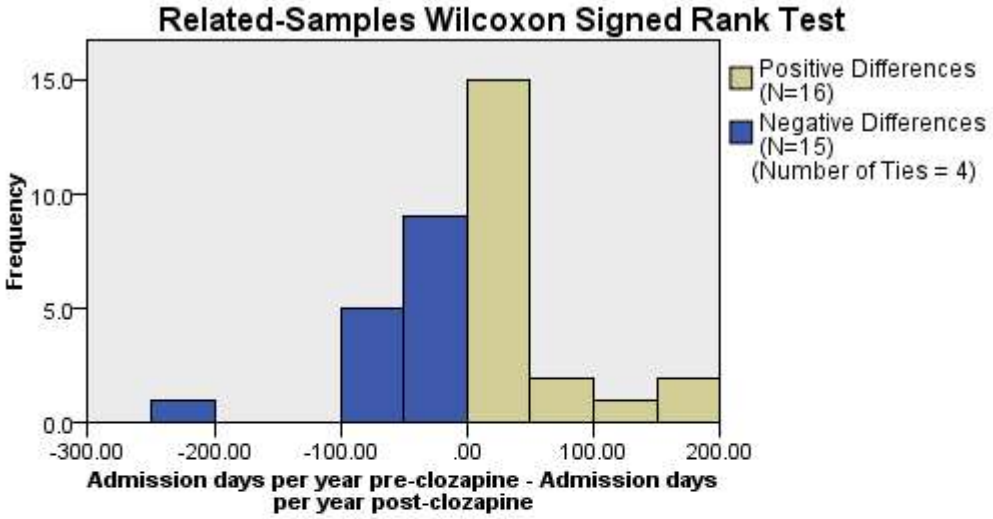


Figure 7-32 Q-Q plot, net change in days of admission per year, analysis method 2, clozapine discontinuers

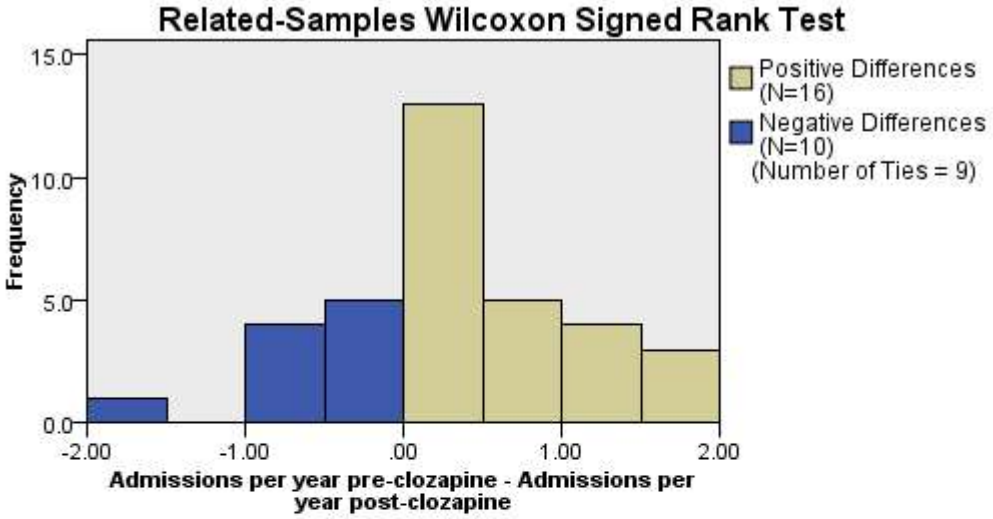
Table 7-67 Paired samples t-test, clozapine discontinuers group, method 2

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Change in days of admission per year	1.42314	70.78564	11.96496	-22.8926	25.73886	0.119	34	0.906
Change in admissions per year	0.25314	.82289	0.13909	-0.02953	0.53582	1.820	34	0.078



Total N	35
Test Statistic	255.000
Standard Error	51.029
Standardized Test Statistic	.137
Asymptotic Sig. (2-sided test)	.891

Figure 7-33 Wilcoxon signed rank test, change in days of admission per year, clozapine discontinuers, analysis method 2



Total N	35
Test Statistic	237.000
Standard Error	39.372
Standardized Test Statistic	1.562
Asymptotic Sig. (2-sided test)	.118

Figure 7-34 Wilcoxon signed rank test, change in admissions per year, clozapine discontinuers, analysis method 2

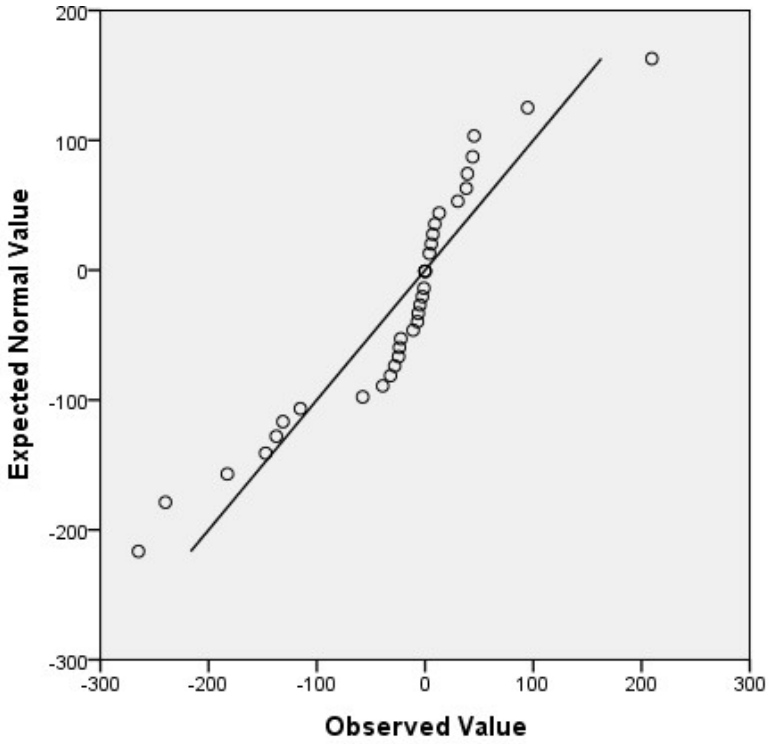
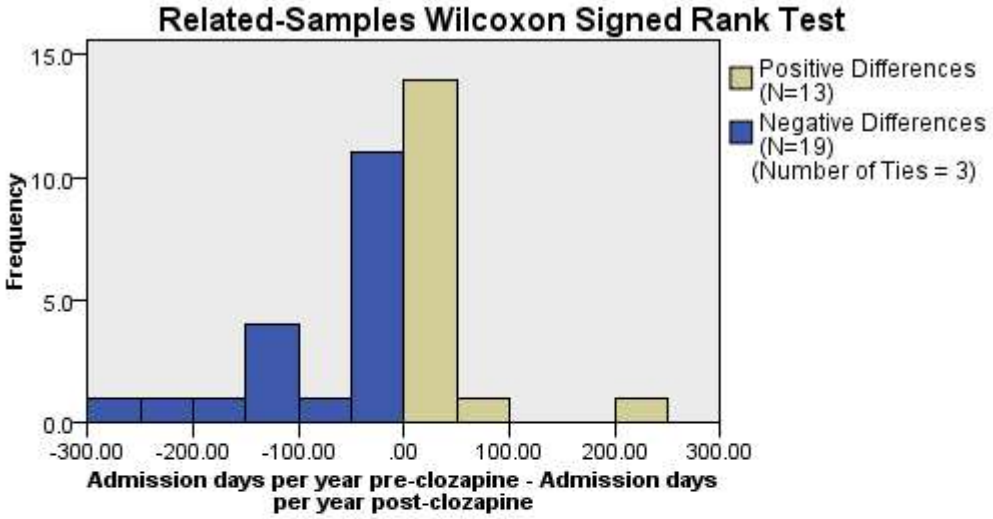


Figure 7-35 Q-Q plot, net change in days of admission per year, analysis method 3, clozapine discontinuers

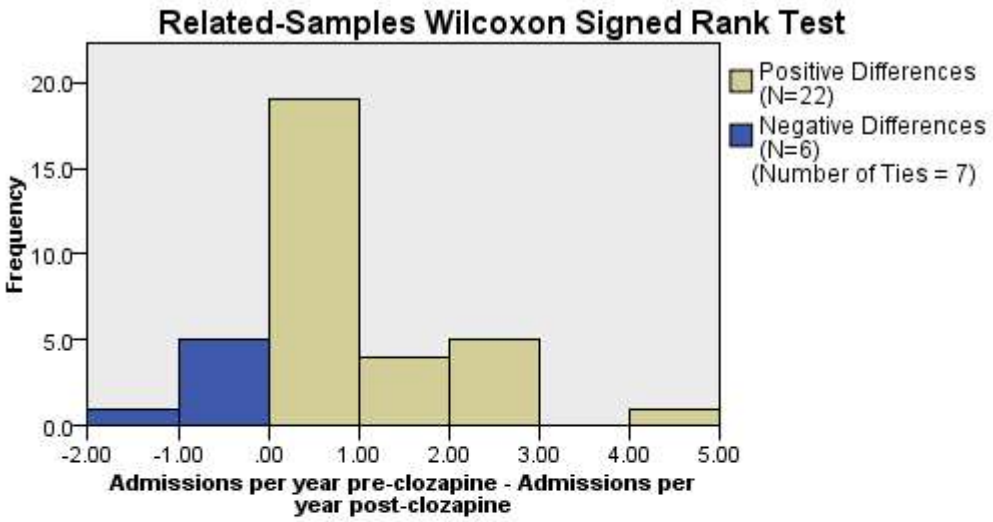
Table 7-68 Paired samples t-test, clozapine discontinuers group, method 3

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Change in days of admission per year	-26.820	90.20094	15.24674	-57.80511	4.1651	-1.759	34	0.088
Change in admissions per year	0.66286	1.16305	0.19659	0.26334	1.0624	3.372	34	0.002



Total N	35
Test Statistic	190.000
Standard Error	53.479
Standardized Test Statistic	-1.384
Asymptotic Sig. (2-sided test)	.166

Figure 7-36 Wilcoxon signed rank test, change in days of admission per year, clozapine discontinuers, analysis method 3



Total N	35
Test Statistic	337.500
Standard Error	43.912
Standardized Test Statistic	3.063
Asymptotic Sig. (2-sided test)	.002

Figure 7-37 Wilcoxon signed rank test, change in admissions per year, clozapine discontinuers, analysis method 3

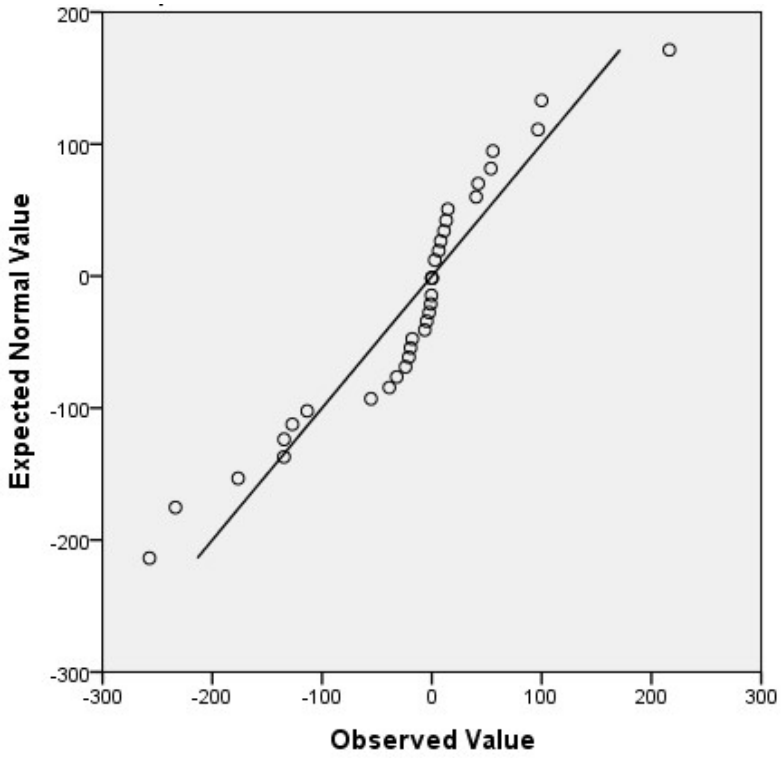
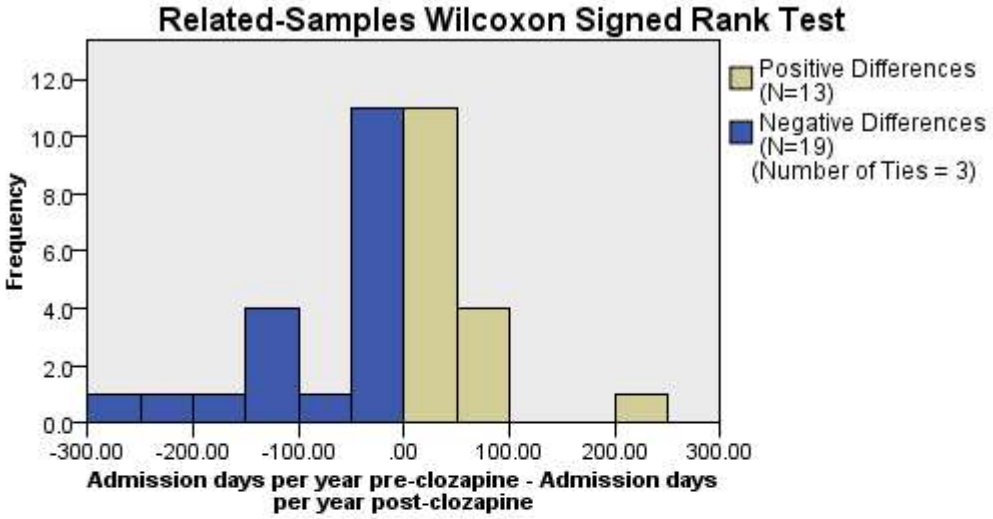


Figure 7-38 Q-Q plot, net change in days of admission per year, analysis method 4, clozapine discontinuers

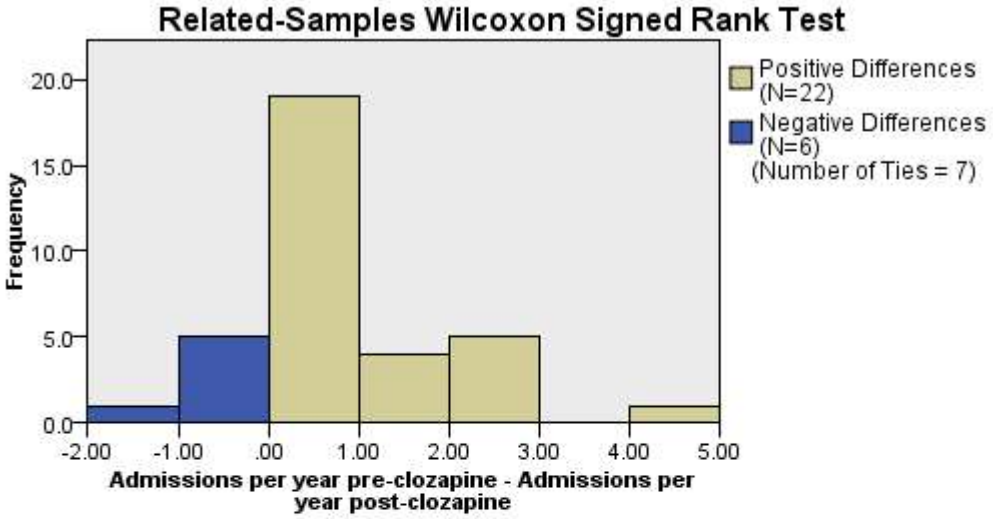
Table 7-69 Paired samples t-test, clozapine discontinuers group, method 4

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Change in days of admission per year	-21.1397	91.56076	15.47659	-52.5919	10.3125	-1.366	34	0.181
Change in admissions per year	0.66286	1.16305	0.19659	0.26334	1.06238	3.372	34	0.002



Total N	35
Test Statistic	204.000
Standard Error	53.479
Standardized Test Statistic	-1.122
Asymptotic Sig. (2-sided test)	.262

Figure 7-39 Wilcoxon signed rank test, change in days of admission per year, clozapine discontinuers, analysis method 4



Total N	35
Test Statistic	337.500
Standard Error	43.912
Standardized Test Statistic	3.063
Asymptotic Sig. (2-sided test)	.002

Figure 7-40 Wilcoxon signed rank test, change in admissions per year, clozapine discontinuers, analysis method 4

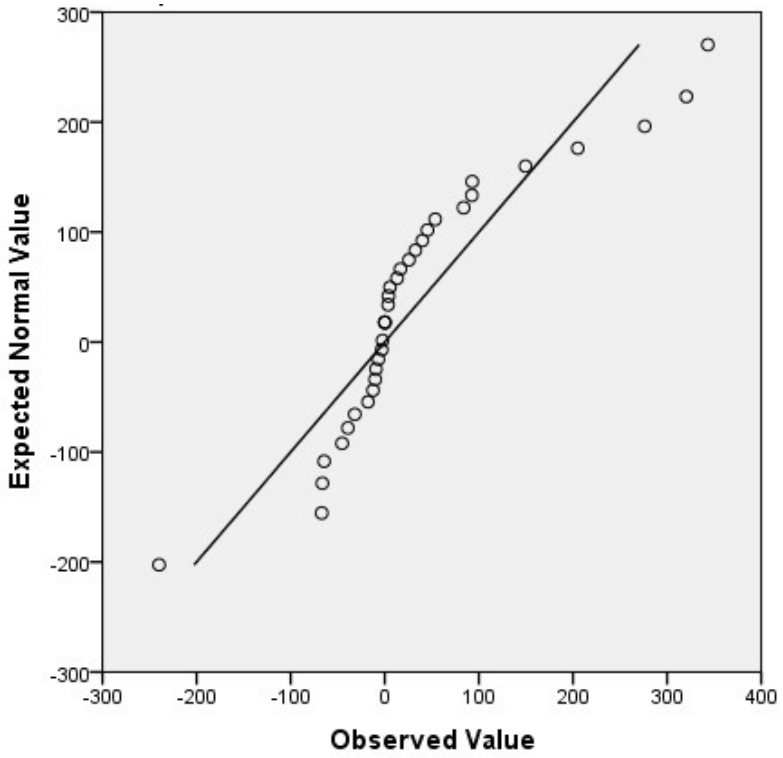
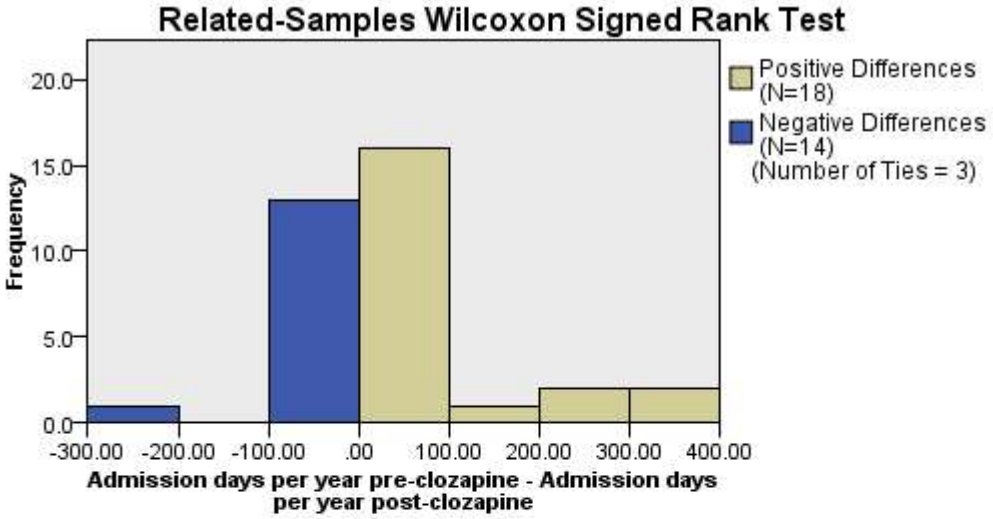


Figure 7-41 Q-Q plot, net change in days of admission per year, analysis method 5, clozapine discontinuers

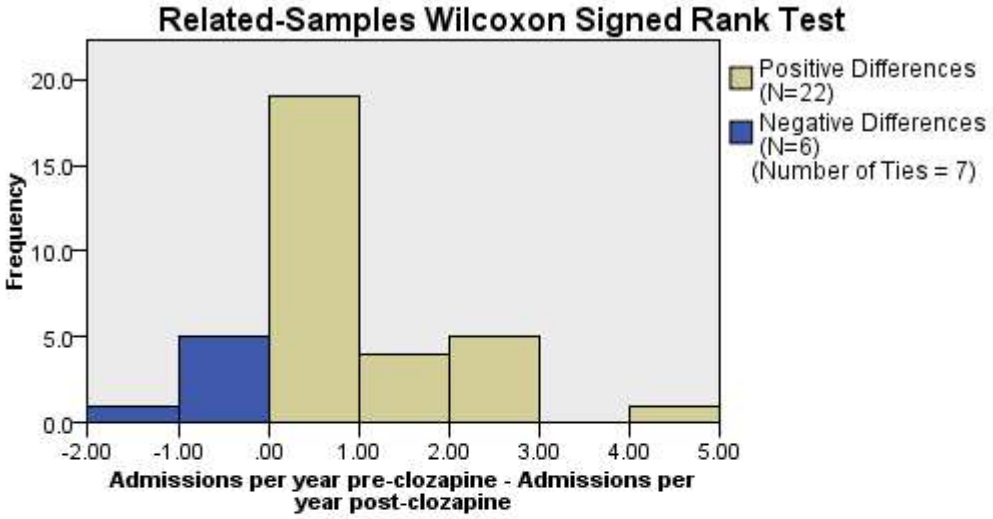
Table 7-70 Paired samples t-test, clozapine discontinuers group, method 5

	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Change in days of admission per year	33.90000	112.43570	19.00510	-4.723	72.52301	1.784	34	0.083
Change in admissions per year	0.66286	1.16305	0.19659	0.26334	1.06238	3.372	34	0.002



Total N	35
Test Statistic	339.000
Standard Error	53.479
Standardized Test Statistic	1.402
Asymptotic Sig. (2-sided test)	.161

Figure 7-42 Wilcoxon signed rank test, change in days of admission per year, clozapine discontinuers, analysis method 5



Total N	35
Test Statistic	337.500
Standard Error	43.912
Standardized Test Statistic	3.063
Asymptotic Sig. (2-sided test)	.002

Figure 7-43 Wilcoxon signed rank test, change in admissions per year, clozapine discontinuers, analysis method 5

Table 7-71 Linear regression model summary, change in days of admission per year, intent to treat group, method 1

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.054	0.003	-0.007	75.80351

Table 7-72 ANOVA, change in days of admission per year, intent to treat group, method 1

	Sum of Squares	df	Mean Square	F	Sig.
Regression	1707.433	1	1707.433	0.297	.587
Residual	574617.198	100	5746.172		
Total	576324.631	101			

Table 7-73 Linear regression coefficients, change in days of admission per year, intent to treat group, method 1

	Unstandardized Coefficients		Standardized Coefficients	T	Sig.
	B	Std. Error	Beta		
Constant	-6.487	9.880		-0.657	0.513
Clozapine theoretical delay	0.892	1.636	0.054	0.545	0.587

Table 7-74 Bootstrapping for coefficients, change in days of admission per year, intent to treat group, method 1

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	-6.487	-0.479	9.981	0.541	-26.071	11.814
Clozapine theoretical delay	0.892	0.099	1.192	0.466	-1.566	3.583

Table 7-75 Linear regression model summary, change in number of admissions per year, intent to treat group, method 1

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.235	0.055	0.046	1.16307

Table 7-76 ANOVA, change in number of admissions per year, intent to treat group, method 1

	Sum of Squares	df	Mean Square	F	Sig.
Regression	7.920	1	7.920	5.855	0.017
Residual	135.272	100	1.353		
Total	143.192	101			

Table 7-77 Linear regression coefficients, change in number of admissions per year, intent to treat group, method 1

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.973	0.152		6.420	<0.0005
Clozapine theoretical delay	-0.061	0.025	-0.235	-2.420	0.017

Table 7-78 Bootstrapping for coefficients, change in number of admissions per year, intent to treat group, method 1

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.973	0.007	0.178	0.001	0.654	1.359
Clozapine theoretical delay	-0.061	-0.002	0.022	0.020	-0.110	-0.025

Table 7-79 Linear regression model summary, change in days of admission per year, intent to treat group, method 2

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.095	0.009	-0.001	57.38544

Table 7-80 ANOVA, change in days of admission per year, intent to treat group, method 2

	Sum of Squares	df	Mean Square	F	Sig.
Regression	2968.447	1	2968.447	0.901	0.345
Residual	329308.882	100	3293.089		
Total	332277.329	101			

Table 7-81 Linear regression coefficients, change in days of admission per year, intent to treat group, method 2

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	21.355	7.480		2.855	0.005
Clozapine theoretical delay	-1.176	1.238	-0.095	-0.949	0.345

Table 7-82 Bootstrap for Coefficients, change in days of admission per year, intent to treat group, method 2

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	21.355	-0.114	7.554	0.007	6.556	35.420
Clozapine theoretical delay	-1.176	0.034	0.910	0.191	-3.115	0.679

Table 7-83 Linear regression model summary, change in number of admissions per year, intent to treat group, method 2

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.112	0.013	0.003	0.64756

Table 7-84 ANOVA, change in number of admissions per year, intent to treat group, method 2

	Sum of Squares	df	Mean Square	F	Sig.
Regression	0.535	1	0.535	1.275	0.261
Residual	41.933	100	0.419		
Total	42.468	101			

Table 7-85 Linear regression coefficients, change in number of admissions per year, intent to treat group, method 2

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.405	0.084		4.796	<0.0005
Clozapine theoretical delay	-0.016	0.014	-0.112	-1.129	0.261

Table 7-86 Bootstrap for Coefficients, change in number of admissions per year, intent to treat group, method 2

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.405	-0.001	0.089	0.001	0.233	0.580
Clozapine theoretical delay	-0.016	<0.0005	0.012	0.203	-0.040	0.007

Table 7-87 Linear regression model summary, change in days of admission per year, intent to treat group, method 3

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.016	< 0.0005	-0.010	76.55247

Table 7-88 ANOVA, change in days of admission per year, intent to treat group, method 3

	Sum of Squares	df	Mean Square	F	Sig.
Regression	154.441	1	154.441	0.026	0.871
Residual	586028.025	100	5860.280		
Total	586182.465	101			

Table 7-89 Linear regression coefficients, change in days of admission per year, intent to treat group, method 3

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	1.370	9.978		0.137	0.891
Clozapine theoretical delay	0.268	1.652	0.016	0.162	0.871

Table 7-90 Bootstrap for Coefficients, change in days of admission per year, intent to treat group, method 3

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	1.370	-0.354	10.371	0.884	-18.511	19.927
Clozapine theoretical delay	0.268	0.072	1.214	0.817	-2.291	2.835

Table 7-91Linear regression model summary, change in days of admission per year, intent to treat group, method 3

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.235	0.055	0.046	1.16307

Table 7-92 ANOVA, change in days of admission per year, intent to treat group, method 3

	Sum of Squares	df	Mean Square	F	Sig.
Regression	7.920	1	7.920	5.855	0.017
Residual	135.272	100	1.353		
Total	143.192	101			

Table 7-93 Linear regression coefficients, change in days of admission per year, intent to treat group, method 3

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.973	0.152		6.420	<0.0005
Clozapine theoretical delay	-0.061	0.025	-0.235	-2.420	0.017

Table 7-94 Bootstrap for Coefficients, change in days of admission per year, intent to treat group, method 3

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.973	-0.007	0.183	0.001	0.661	1.307
Clozapine theoretical delay	-0.061	<0.0005	0.022	0.027	-0.116	-0.021

Table 7-95 Linear regression model summary, change in days of admission per year, intent to treat group, method 4

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.019	<0.0005	-0.010	79.75255

Table 7-96 ANOVA, change in days of admission per year, intent to treat group, method 4

	Sum of Squares	df	Mean Square	F	Sig.
Regression	237.574	1	237.574	0.037	0.847
Residual	636046.884	100	6360.469		
Total	636284.458	101			

Table 7-97 Linear regression coefficients, change in days of admission per year, intent to treat group, method 4

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	9.284	10.395		0.893	0.374
Clozapine theoretical delay	-0.333	1.721	-0.019	-0.193	0.847

Table 7-98 Bootstrap for Coefficients, change in days of admission per year, intent to treat group, method 4

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	9.284	-0.150	10.961	0.402	-11.374	30.498
Clozapine theoretical delay	-0.333	0.030	1.285	0.820	-3.028	2.254

Table 7-99 Linear regression model summary, change in number of admissions per year, intent to treat group, method 4

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.235	0.055	0.046	1.16307

Table 7-100 ANOVA, change in number of admissions per year, intent to treat group, method 4

	Sum of Squares	df	Mean Square	F	Sig.
Regression	7.920	1	7.920	5.855	0.017
Residual	135.272	100	1.353		
Total	143.192	101			

Table 7-101 Linear regression coefficients, change in number of admissions per year, intent to treat group, method 4

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.973	0.152		6.420	<0.0005
Clozapine theoretical delay	-0.061	0.025	-0.235	-2.420	0.017

Table 7-102 Bootstrap for Coefficients, change in number of admissions per year, intent to treat group, method 4

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.973	-0.006	0.184	0.002	0.651	1.313
Clozapine theoretical delay	-0.061	<0.0005	0.023	0.025	-0.117	-0.018

Table 7-103 Linear regression model summary, change in days of admission per year, intent to treat group, method 5

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.208	0.043	0.034	91.24355

Table 7-104 ANOVA, change in days of admission per year, intent to treat group, method 5

	Sum of Squares	df	Mean Square	F	Sig.
Regression	37478.189	1	37478.189	4.502	0.036
Residual	832538.572	100	8325.386		
Total	870016.761	101			

Table 7-105 Linear regression coefficients, change in days of admission per year, intent to treat group, method 5

	Unstandardized Coefficients		Standardized Coefficients	T	Sig.
	B	Std. Error	Beta		
Constant	63.723	11.893		5.358	<0.0005
Clozapine theoretical delay	-4.178	1.969	-0.208	-2.122	0.036

Table 7-106 Bootstrap for Coefficients, change in days of admission per year, intent to treat group, method 5

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	63.723	-0.099	13.325	0.002	38.464	90.419
Clozapine theoretical delay	-4.178	-0.016	1.507	0.017	-7.459	-1.210

Table 7-107 Linear regression model summary, change in number of admissions per year, intent to treat group, method 5

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.235	0.055	0.046	1.16307

Table 7-108 ANOVA, change in number of admissions per year, intent to treat group, method 5

	Sum of Squares	df	Mean Square	F	Sig.
Regression	7.920	1	7.920	5.855	0.017
Residual	135.272	100	1.353		
Total	143.192	101			

Table 7-109 Linear regression coefficients, change in number of admissions per year, intent to treat group, method 5

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.973	0.152		6.420	<0.0005
Clozapine theoretical delay	-0.061	0.025	-0.235	-2.420	0.017

Table 7-110 Bootstrap for Coefficients, change in number of admissions per year, intent to treat group, method 5

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.973	-0.001	0.183	0.001	0.662	1.310
Clozapine theoretical delay	-0.061	-0.001	0.022	0.028	-0.113	-0.023

Table 7-111 Linear regression model summary, change in days of admission per year, clozapine continuers group, method 1

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.065	0.004	-0.011	62.46892

Table 7-112 ANOVA, change in days of admission per year, clozapine continuers group, method 1

	Sum of Squares	df	Mean Square	F	Sig.
Regression	1068.707	1	1068.707	0.274	0.603
Residual	253653.751	65	3902.365		
Total	254722.459	66			

Table 7-113 Linear regression coefficients, change in days of admission per year, clozapine continuers group, method 1

	Unstandardized Coefficients		Standardized Coefficients	T	Sig.
	B	Std. Error	Beta		
Constant	8.776	10.304		0.852	0.398
Clozapine theoretical delay	0.876	1.674	0.065	0.523	0.603

Table 7-114 Bootstrap for Coefficients, change in days of admission per year, clozapine continuers group, method 1

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	8.776	-0.092	10.489	0.422	-12.432	28.414
Clozapine theoretical delay	0.876	-0.016	1.141	0.443	-1.382	3.127

Table 7-115 Linear regression model summary, change in number of admissions per year, clozapine continuers group, method 1

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.198	0.039	0.024	1.19719

Table 7-116 ANOVA, change in number of admissions per year, clozapine continuers group, method 1

	Sum of Squares	df	Mean Square	F	Sig.
Regression	3.791	1	3.791	2.645	0.109
Residual	93.163	65	1.433		
Total	96.954	66			

Table 7-117 Linear regression coefficients, change in number of admissions per year, clozapine continuers group, method 1

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.988	0.197		5.004	<0.0005
Clozapine theoretical delay	-0.052	0.032	-0.198	-1.626	0.109

Table 7-118 Bootstrap for Coefficients, change in number of admissions per year, clozapine continuers group, method 1

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.988	0.004	0.247	0.015	0.573	1.517
Clozapine theoretical delay	-0.052	-0.002	0.031	0.140	-0.126	-0.004

Table 7-119 Linear regression model summary, change in days of admission per year, clozapine continuers group, method 2

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.046	0.002	-0.013	47.89324

Table 7-120 ANOVA, change in days of admission per year, clozapine continuers group, method 2

	Sum of Squares	df	Mean Square	F	Sig.
Regression	322.159	1	322.159	0.140	0.709
Residual	149094.555	65	2293.762		
Total	149416.714	66			

Table 7-121 Linear regression coefficients, change in days of admission per year, clozapine continuers group, method 2

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	26.727	7.900		3.383	0.001
Clozapine theoretical delay	-0.481	1.284	-0.046	-0.375	0.709

Table 7-122 Bootstrap for Coefficients, change in days of admission per year, clozapine continuers group, method 2

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	26.727	0.525	7.603	0.002	12.496	43.851
Clozapine theoretical delay	-0.481	-0.082	0.921	0.590	-2.347	1.067

Table 7-123 Linear regression model summary, change in number of admissions per year, clozapine continuers group, method 2

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.127	0.016	0.001	.24378

Table 7-124 ANOVA, change in number of admissions per year, clozapine continuers group, method 2

	Sum of Squares	df	Mean Square	F	Sig.
Regression	0.063	1	0.063	1.059	0.307
Residual	3.863	65	0.059		
Total	3.926	66			

Table 7-125 Linear regression coefficients, change in number of admissions per year, clozapine continuers group, method 2

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.081	0.040		2.003	0.049
Clozapine theoretical delay	0.007	0.007	0.127	1.029	0.307

Table 7-126 Bootstrap for Coefficients, change in number of admissions per year, clozapine continuers group, method 2

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.081	-0.001	0.034	0.027	0.023	0.146
Clozapine theoretical delay	0.007	<0.0005	0.007	0.317	-0.004	0.021

Table 7-127 Linear regression model summary, change in days of admission per year, clozapine continuers group, method 3

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.015	<0.0005	-0.015	63.72243

Table 7-128 ANOVA, change in days of admission per year, clozapine continuers group, method 3

	Sum of Squares	df	Mean Square	F	Sig.
Regression	57.193	1	57.193	0.014	0.906
Residual	263935.612	65	4060.548		
Total	263992.805	66			

Table 7-129 Linear regression coefficients, change in days of admission per year, clozapine continuers group, method 3

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	16.861	10.511		1.604	0.114
Clozapine theoretical delay	0.203	1.708	0.015	0.119	0.906

Table 7-130 Bootstrap for coefficients, change in days of admission per year, clozapine continuers, method 3

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	16.861	-0.038	10.872	0.131	-4.907	36.290
Clozapine theoretical delay	0.203	-0.041	1.207	0.858	-2.349	2.469

Table 7-131 Linear regression model summary, change in number of admissions per year, clozapine continuers group, method 3

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.198	0.039	0.024	1.19719

Table 7-132 ANOVA, change in number of admissions per year, clozapine continuers group, method 3

	Sum of Squares	df	Mean Square	F	Sig.
Regression	3.791	1	3.791	2.645	0.109
Residual	93.163	65	1.433		
Total	96.954	66			

Table 7-133 Linear regression coefficients, change in number of admissions per year, clozapine continuers group, method 3

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.988	0.197		5.004	<0.0005
Clozapine theoretical delay	-0.052	0.032	-0.198	-1.626	0.109

Table 7-134 Bootstrap for coefficients, change in number of admissions per year, clozapine continuers, method 3

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.988	0.003	0.247	0.015	0.606	1.482
Clozapine theoretical delay	-0.052	-0.002	0.031	0.142	-0.129	-0.005

Table 7-135 Linear regression model summary, change in days of admission per year, clozapine continuers group, method 4

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.030	0.001	-0.014	68.58996

Table 7-136 ANOVA, change in days of admission per year, clozapine continuers group, method 4

	Sum of Squares	df	Mean Square	F	Sig.
Regression	276.130	1	276.130	0.059	0.809
Residual	305797.858	65	4704.582		
Total	306073.987	66			

Table 7-137 Linear regression coefficients, change in days of admission per year, clozapine continuers group, method 4

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	25.030	11.314		2.212	0.030
Clozapine theoretical delay	-0.445	1.839	-0.030	-0.242	0.809

Table 7-138 Bootstrap for Coefficients, change in days of admission per year, clozapine continuers group, method 4

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	25.030	-0.334	12.486	0.056	-.318	48.063
Clozapine theoretical delay	-0.445	-0.012	1.403	0.760	-3.181	2.220

Table 7-139 Linear regression model summary, change in number of admissions per year, clozapine continuers group, method 4

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.198	0.039	0.024	1.19719

Table 7-140 ANOVA, change in number of admissions per year, clozapine continuers group, method 4

	Sum of Squares	df	Mean Square	F	Sig.
Regression	3.791	1	3.791	2.645	0.109
Residual	93.163	65	1.433		
Total	96.954	66			

Table 7-141 Linear regression coefficients, change in number of admissions per year, clozapine continuers group, method 4

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.988	0.197		5.004	<0.0005
Clozapine theoretical delay	-0.052	0.032	-0.198	-1.626	0.109

Table 7-142 Bootstrap for Coefficients, change in number of admissions per year, clozapine continuers group, method 4

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.988	0.007	0.247	0.016	0.603	1.546
Clozapine theoretical delay	-0.052	-0.003	0.031	0.153	-0.127	-0.005

Table 7-143 Linear regression model summary, change in days of admission per year, clozapine continuers group, method 5

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.196	0.038	0.024	79.81468

Table 7-144 ANOVA, change in days of admission per year, clozapine continuers group, method 5

	Sum of Squares	df	Mean Square	F	Sig.
Regression	16537.610	1	16537.610	2.596	0.112
Residual	414074.892	65	6370.383		
Total	430612.502	66			

Table 7-145 Linear regression coefficients, change in days of admission per year, clozapine continuers group, method 5

	B	Std. Error	Beta	t	Sig.
Constant	68.574	13.165		5.209	<0.0005
Clozapine theoretical delay	-3.447	2.139	-0.196	-1.611	0.112

Table 7-146 Bootstrap for Coefficients, change in days of admission per year, clozapine continuers group, method 5

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	68.574	0.438	15.849	0.003	39.831	102.445
Clozapine theoretical delay	-3.447	-0.152	1.896	0.079	-7.647	-0.431

Table 7-147 Linear regression model summary, change in number of admissions per year, clozapine continuers group, method 5

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.198	0.039	0.024	1.19719

Table 7-148 ANOVA, change in number of admissions per year, clozapine continuers group, method 5

	Sum of Squares	df	Mean Square	F	Sig.
Regression	3.791	1	3.791	2.645	0.109
Residual	93.163	65	1.433		
Total	96.954	66			

Table 7-149 Linear regression coefficients, change in number of admissions per year, clozapine continuers group, method 5

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.988	0.197		5.004	<0.0005
Clozapine theoretical delay	-0.052	0.032	-0.198	-1.626	0.109

Table 7-150 Bootstrap for Coefficients, change in number of admissions per year, clozapine continuers group, method 5

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.988	<0.0005	0.246	0.017	0.597	1.451
Clozapine theoretical delay	-0.052	-0.002	0.032	0.150	-0.127	-0.002

Table 7-151 Linear regression model summary, change in days of admission per year, clozapine discontinuers group, method 1

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.005	<0.0005	-0.030	91.35137

Table 7-152 ANOVA, change in days of admission per year, clozapine discontinuers group, method 1

	Sum of Squares	df	Mean Square	F	Sig.
Regression	7.018	1	7.018	0.001	0.977
Residual	275387.383	33	8345.072		
Total	275394.401	34			

Table 7-153 Linear regression coefficients, change in days of admission per year, clozapine discontinuers group, method 1

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	-32.775	19.436		-1.686	0.101
Clozapine theoretical delay	0.097	3.343	0.005	0.029	0.977

Table 7-154 Bootstrap for coefficients, change in days of admission per year, clozapine discontinuers group, method 1

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	-32.775	-1.958	19.209	0.109	-71.884	-1.083
Clozapine theoretical delay	0.097	0.349	2.181	0.970	-4.642	5.594

Table 7-155 Linear regression model summary, change in number of admissions per year, clozapine discontinuers group, method 1

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.320	0.102	0.075	1.11810

Table 7-156 ANOVA, change in number of admissions per year, clozapine discontinuers group, method 1

	Sum of Squares	df	Mean Square	F	Sig.
Regression	4.707	1	4.707	3.765	0.061
Residual	41.255	33	1.250		
Total	45.961	34			

Table 7-157 Linear regression coefficients, change in number of admissions per year, clozapine discontinuers group, method 1

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.943	0.238		3.964	<0.0005
Clozapine theoretical delay	-0.079	0.041	-0.320	-1.940	0.061

Table 7-158 Bootstrap for coefficients, change in number of admissions per year, clozapine discontinuers group, method 1

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.943	0.012	0.265	0.005	0.454	1.510
Clozapine theoretical delay	-0.079	-0.006	0.038	0.027	-0.170	-0.031

Table 7-159 Linear regression model summary, change in days of admission per year, clozapine discontinuers group, method 2

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.193	0.037	0.008	70.49758

Table 7-160 ANOVA, change in days of admission per year, clozapine discontinuers group, method 2

	Sum of Squares	df	Mean Square	F	Sig.
Regression	6356.659	1	6356.659	1.279	0.266
Residual	164007.010	33	4969.909		
Total	170363.669	34			

Table 7-161 Linear regression coefficients, change in days of admission per year, clozapine discontinuers group, method 2

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	11.724	14.999		0.782	0.440
Clozapine theoretical delay	-2.918	2.580	-0.193	-1.131	0.266

Table 7-162 Bootstrap for coefficients, change in days of admission per year, clozapine discontinuers group, method 2

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	11.724	-0.018	15.242	0.463	-19.603	41.512
Clozapine theoretical delay	-2.918	-0.051	1.669	0.093	-6.469	-0.127

Table 7-163 Linear regression model summary, change in number of admissions per year, clozapine discontinuers group, method 2

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.136	0.019	-0.011	0.53113

Table 7-164 ANOVA, change in number of admissions per year, clozapine discontinuers group, method 2

	Sum of Squares	df	Mean Square	F	Sig.
Regression	0.176	1	0.176	0.623	0.436
Residual	9.309	33	0.282		
Total	9.485	34			

Table 7-165 Linear regression coefficients, change in number of admissions per year, clozapine discontinuers group, method 2

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.359	0.113		3.179	0.003
Clozapine theoretical delay	0.015	0.019	0.136	0.789	0.436

Table 7-166 Bootstrap for coefficients, change in number of admissions per year, clozapine discontinuers group, method 2

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.359	-0.002	0.119	0.024	0.162	0.593
Clozapine theoretical delay	0.015	0.002	0.016	0.376	-0.014	0.051

Table 7-167 Linear regression model summary, change in days of admission per year, clozapine discontinuers group, method 3

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.023	0.001	-0.030	91.53356

Table 7-168 ANOVA, change in days of admission per year, clozapine discontinuers group, method 3

	Sum of Squares	df	Mean Square	F	Sig.
Regression	141.064	1	141.064	0.017	0.898
Residual	276486.977	33	8378.393		
Total	276628.041	34			

Table 7-169 Linear regression coefficients, change in days of admission per year, clozapine discontinuers group, method 3

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	-25.284	19.475		-1.298	0.203
Clozapine theoretical delay	-0.435	3.350	-0.023	-0.130	0.898

Table 7-170 Bootstrap for coefficients, change in days of admission per year, clozapine discontinuers group, method 3

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	-25.284	-1.970	19.101	0.194	-64.528	5.910
Clozapine theoretical delay	-0.435	0.304	2.154	0.842	-5.171	4.694

Table 7-171 Linear regression model summary, change in number of admissions per year, clozapine discontinuers group, method 3

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.320	0.102	0.075	1.11810

Table 7-172 ANOVA, change in number of admissions per year, clozapine discontinuers group, method 3

	Sum of Squares	df	Mean Square	F	Sig.
Regression	4.707	1	4.707	3.765	0.061
Residual	41.255	33	1.250		
Total	45.961	34			

Table 7-173 Linear regression coefficients, change in number of admissions per year, clozapine discontinuers group, method 3

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.943	0.238		3.964	<0.0005
Clozapine theoretical delay	-0.079	0.041	-0.320	-1.940	0.061

Table 7-174 Bootstrap for coefficients, change in number of admissions per year, clozapine discontinuers group, method 3

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.943	0.001	0.263	0.005	0.457	1.460
Clozapine theoretical delay	-0.079	-0.005	0.037	0.026	-0.171	-0.028

Table 7-175 Linear regression model summary, change in days of admission per year, clozapine discontinuers group, method 4

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.049	0.002	-0.028	92.82800

Table 7-176 ANOVA, change in days of admission per year, clozapine discontinuers group, method 4

	Sum of Squares	df	Mean Square	F	Sig.
Regression	674.788	1	674.788	0.078	0.781
Residual	284362.227	33	8617.037		
Total	285037.014	34			

Table 7-177 Linear regression coefficients, change in days of admission per year, clozapine discontinuers group, method 4

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	-17.783	19.750		-0.900	0.374
Clozapine theoretical delay	-0.951	3.397	-0.049	-0.280	0.781

Table 7-178 Bootstrap for coefficients, change in days of admission per year, clozapine discontinuers group, method 4

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	-17.783	-0.469	20.550	0.406	-59.192	20.119
Clozapine theoretical delay	-0.951	0.140	2.323	0.662	-6.453	4.577

Table 7-179 Linear regression model summary, change in number of admissions per year, clozapine discontinuers group, method 4

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.320	0.102	0.075	1.11810

Table 7-180 ANOVA, change in number of admissions per year, clozapine discontinuers group, method 4

	Sum of Squares	df	Mean Square	F	Sig.
Regression	4.707	1	4.707	3.765	0.061
Residual	41.255	33	1.250		
Total	45.961	34			

Table 7-181 Linear regression coefficients, change in number of admissions per year, clozapine discontinuers group, method 4

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.943	0.238		3.964	<0.0005
Clozapine theoretical delay	-0.079	0.041	-0.320	-1.940	0.061

Table 7-182 Bootstrap for coefficients, change in number of admissions per year, clozapine discontinuers group, method 4

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.943	0.019	0.277	0.003	0.404	1.551
Clozapine theoretical delay	-0.079	-0.007	0.041	0.031	-0.159	-0.033

Table 7-183 Linear regression model summary, change in days of admission per year, clozapine discontinuers group, method 5

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.249	0.062	0.033	110.53921

Table 7-184 ANOVA, change in days of admission per year, clozapine discontinuers group, method 5

	Sum of Squares	df	Mean Square	F	Sig.
Regression	26592.130	1	26592.130	2.176	0.150
Residual	403224.229	33	12218.916		
Total	429816.360	34			

Table 7-185 Linear regression coefficients, change in days of admission per year, clozapine discontinuers group, method 5

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	54.970	23.518		2.337	0.026
Clozapine theoretical delay	-5.968	4.045	-0.249	-1.475	0.150

Table 7-186 Bootstrap for coefficients, change in days of admission per year, clozapine discontinuers group, method 5

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	54.970	2.912	24.807	0.046	3.113	116.499
Clozapine theoretical delay	-5.968	-0.602	2.912	0.034	-11.913	-2.213

Table 7-187 Linear regression model summary, change in number of admissions per year, clozapine discontinuers group, method 5

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.320	0.102	0.075	1.11810

Table 7-188 ANOVA, change in number of admissions per year, clozapine discontinuers group, method 5

	Sum of Squares	df	Mean Square	F	Sig.
Regression	4.707	1	4.707	3.765	0.061
Residual	41.255	33	1.250		
Total	45.961	34			

Table 7-189 Linear regression coefficients, change in number of admissions per year, clozapine discontinuers group, method 5

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
Constant	0.943	0.238		3.964	<0.0005
Clozapine theoretical delay	-0.079	0.041	-0.320	-1.940	0.061

Table 7-190 Bootstrap for coefficients, change in number of admissions per year, clozapine discontinuers group, method 5

	B	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	BCa 95% Confidence Interval	
					Lower	Upper
Constant	0.943	0.031	0.263	0.008	0.415	1.588
Clozapine theoretical delay	-0.079	-0.009	0.038	0.028	-0.160	-0.038

Table 7-191 MANOVA patient demographics, intent to treat group

	Category	*N*
Gender	Male	64
	Female	38
Age	20 - 29	17
	30 - 39	37
	40 - 49	38
	50 -59	8
	60 - 69	1
	70 - 79	1
Ethnicity	White	45
	Black	38
	Asian	9
	Mixed	7
	Other	3
Diagnosis	F20	68
	F25	17
	F31	6
	Other	11
Clozapine continuer or discontinuer	Continuer	67
	Discontinuer	35
Total number of antipsychotics pre-clozapine	1 - 2	16
	3 - 5	49
	6 - 10	27
	11 +	10

Table 7-192 MANOVA test for equality of covariance matrices, intent to treat group

Box's M	16.046
F	1.087
df1	9
df2	686.575
Sig.	0.370

Table 7-193 MANOVA test statistics, intent to treat group

Effect		**Value**	**F**	**Hypothesis df**	**Error df**	**Sig.**
Intercept	Pillai's Trace	0.382	5.861	2.000	19.000	0.010
	Wilks' Lambda	0.618	5.861	2.000	19.000	0.010
	Hotelling's Trace	0.617	5.861	2.000	19.000	0.010
	Roy's Largest Root	0.617	5.861	2.000	19.000	0.010
Gender	Pillai's Trace	0.065	0.659	2.000	19.000	0.529
	Wilks' Lambda	0.935	0.659	2.000	19.000	0.529
	Hotelling's Trace	0.069	0.659	2.000	19.000	0.529
	Roy's Largest Root	0.069	0.659	2.000	19.000	0.529
Age	Pillai's Trace	0.727	2.283	10.000	40.000	0.032
	Wilks' Lambda	0.398	2.220	10.000	38.000	0.038
	Hotelling's Trace	1.196	2.152	10.000	36.000	0.045
	Roy's Largest Root	0.806	3.223	5.000	20.000	0.027
Ethnicity	Pillai's Trace	0.266	0.768	8.000	40.000	0.633
	Wilks' Lambda	0.736	0.788	8.000	38.000	0.616
	Hotelling's Trace	0.357	0.803	8.000	36.000	0.604
	Roy's Largest Root	0.350	1.750	4.000	20.000	0.179
Diagnosis	Pillai's Trace	0.149	0.536	6.000	40.000	0.777
	Wilks' Lambda	0.855	0.516	6.000	38.000	0.793
	Hotelling's Trace	0.165	0.495	6.000	36.000	0.808
	Roy's Largest Root	0.129	0.859	3.000	20.000	0.478
Clozapine continuer or discontinuer	Pillai's Trace	0.224	2.750	2.000	19.000	0.089
	Wilks' Lambda	0.776	2.750	2.000	19.000	0.089
	Hotelling's Trace	0.289	2.750	2.000	19.000	0.089
	Roy's Largest Root	0.289	2.750	2.000	19.000	0.089
Total number of antipsychotics pre-clozapine	Pillai's Trace	0.357	1.446	6.000	40.000	0.221
	Wilks' Lambda	0.674	1.381	6.000	38.000	0.247
	Hotelling's Trace	0.438	1.315	6.000	36.000	0.275
	Roy's Largest Root	0.272	1.815	3.000	20.000	0.177

Table 7-194 MANOVA Levene's test of equality of error variances, intent to treat group

	F	df1	df2	Sig.
Net change in days of admission per year	2.432	81	20	0.014
Net change in number of admissions per year	1.536	81	20	0.139

Table 7-195 ANOVA summary table, intent to treat group

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	Net change in days of admission	291115.477	81	3594.018	1.746	0.079
	Net change in number of admissions	36.769	81	0.454	1.593	0.119
Intercept	Net change in days of admission	3879.570	1	3879.570	1.885	0.185
	Net change in number of admissions	3.163	1	3.163	11.100	0.003
Gender	Net change in days of admission	2853.128	1	2853.128	1.386	0.253
	Net change in number of admissions	0.182	1	0.182	0.639	0.433
Age	Net change in days of admission	32649.207	5	6529.841	3.173	0.029
	Net change in number of admissions	2.868	5	0.574	2.013	0.120
Ethnicity	Net change in days of admission	2014.601	4	503.650	0.245	0.909
	Net change in number of admissions	0.472	4	0.118	0.414	0.796
Diagnosis	Net change in days of admission	5231.681	3	1743.894	0.847	0.484
	Net change in number of admissions	0.367	3	0.122	0.430	0.734
Clozapine continuer or discontinuer	Net change in days of admission	11348.115	1	11348.115	5.514	0.029
	Net change in number of admissions	1.082	1	1.082	3.796	0.066
Total number of antipsychotics pre-clozapine	Net change in days of admission	7428.049	3	2476.016	1.203	0.334
	Net change in number of admissions	1.480	3	0.493	1.732	0.193
Residual sum of squares	Net change in days of admission	41161.853	20	2058.093		

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
	Net change in number of admissions	5.699	20	0.285		
Total	Net change in days of admission	360850.836	102			
	Net change in number of admissions	54.457	102			
Total sums of squares	Net change in days of admission	332277.329	101			
	Net change in number of admissions	42.468	101			

Table 7-196 MANOVA eigenvalues, age variable, intent to treat group

Variate	Eigenvalue	% of Variance	Cumulative %	Canonical Correlation
1	0.105	91.4	91.4	0.309
2	0.010	8.6	100.0	0.099

Table 7-197 MANOVA, significance tests for variates, age variable, intent to treat group

Test of variate(s)	Wilks' Lambda	Chi-square	df	Sig.
1 through 2	0.896	10.672	10	0.384
2	0.990	0.954	4	0.917

Table 7-198 MANOVA, canonical variate correlation coefficients, age variable, intent to treat group

	Variate	
	1	2
Net change in days of admission per year	0.996	0.090
Net change in number of admissions per year	0.522	0.853

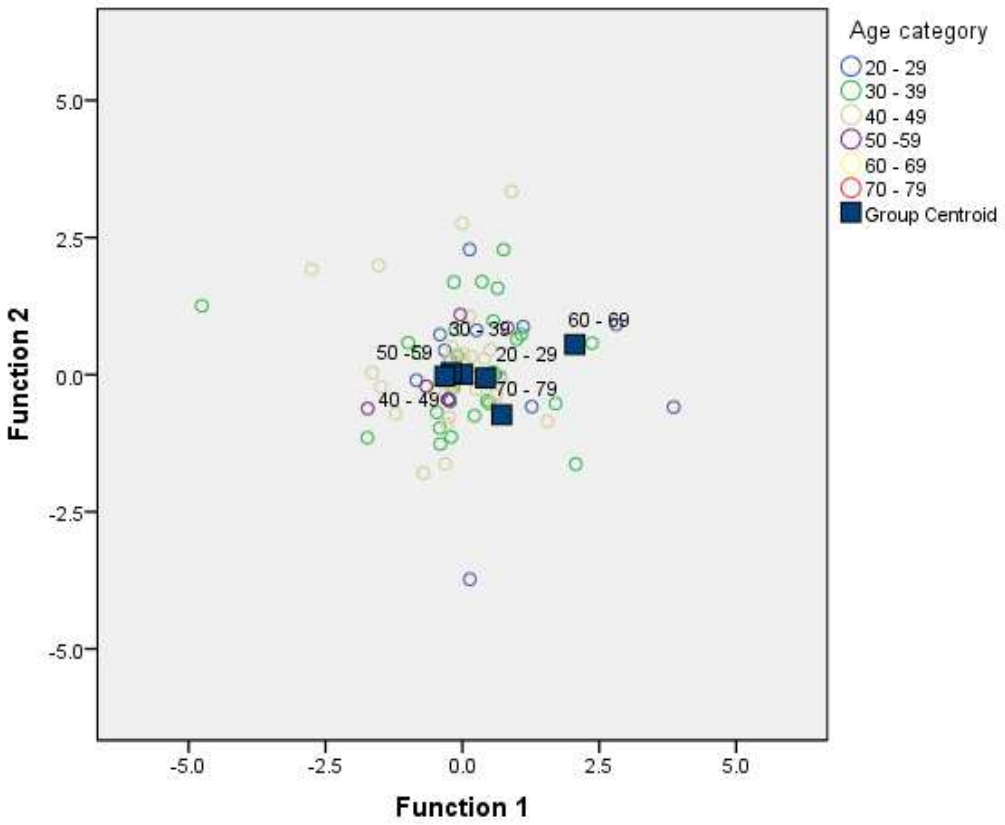


Figure 7-44 MANOVA, combined group plot, age variable, intent to treat group

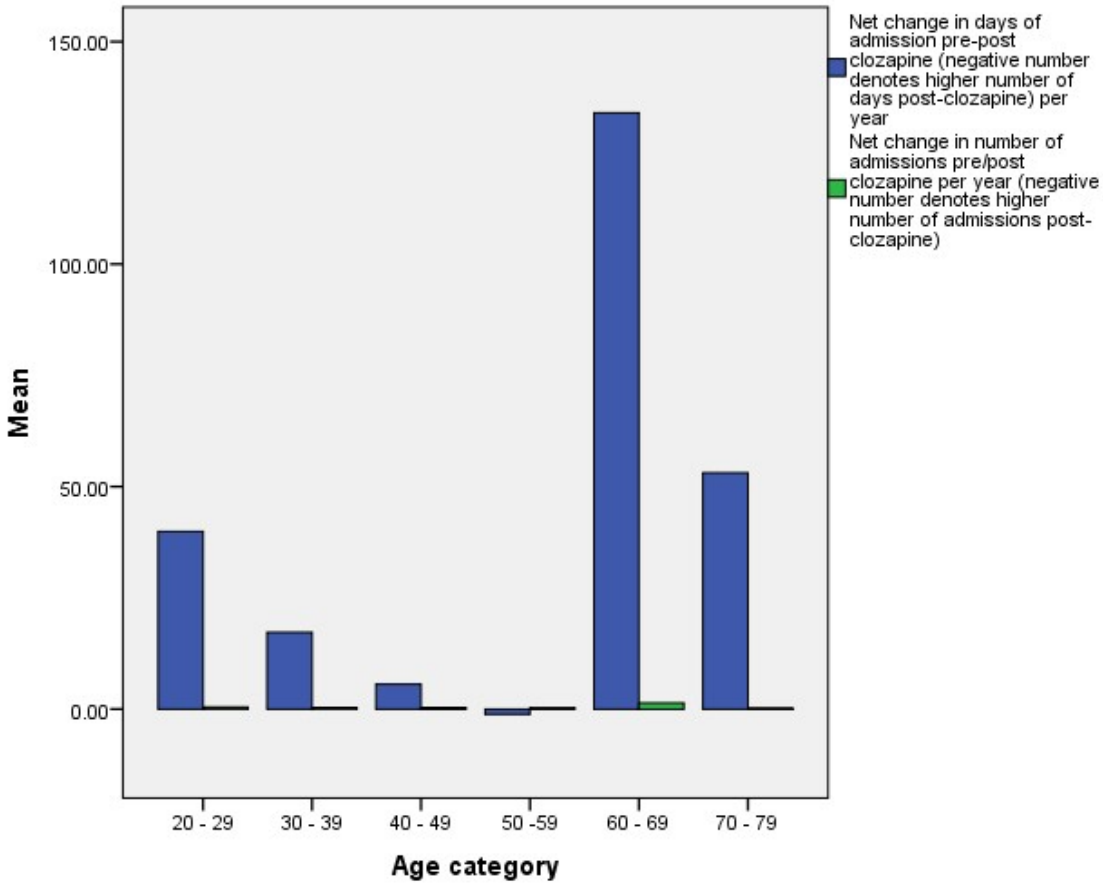


Figure 7-45 MANOVA histogram, age variable, intent to treat group

Table 7-199 MANOVA patient demographics, age variable combined, intent to treat group

		Value Label	*N*
Age category	1	20 - 29	17
	2	30 - 39	37
	3	40 - 49	38
	4	> 50	10
Gender	1	Male	64
	2	Female	38
Ethnicity category	1	White	45
	2	Black	38
	3	Asian	9
	4	Mixed	7
	5	Other	3
Diagnosis	1	F20	68
	2	F25	17
	3	F31	6
	4	Other	11
Total number of antipsychotics pre-clozapine category	1	1 - 2	16
	2	3 - 5	49
	3	6 - 10	27
	4	11 +	10
Clozapine continuer or discontinuer	0	Continuer	67
	1	Discontinuer	35

Table 7-200 MANOVA test for equality of covariance matrices, age variable combined, intent to treat group

Box's M	16.046
F	1.087
df1	9
df2	686.575
Sig.	.370

Table 7-201 MANOVA test statistics, age variable combined, intent to treat group

Effect		Value	F	Hypothesis df	Error df	Sig.
Intercept	Pillai's Trace	0.413	6.671	2.000	19.000	0.006
	Wilks' Lambda	0.587	6.671	2.000	19.000	0.006
	Hotelling's Trace	0.702	6.671	2.000	19.000	0.006
	Roy's Largest Root	0.702	6.671	2.000	19.000	0.006
Age	Pillai's Trace	0.553	2.545	6.000	40.000	0.035
	Wilks' Lambda	0.500	2.620	6.000	38.000	0.032
	Hotelling's Trace	0.893	2.678	6.000	36.000	0.030
	Roy's Largest Root	0.752	5.014	3.000	20.000	0.009
Gender	Pillai's Trace	0.094	0.990	2.000	19.000	0.390
	Wilks' Lambda	0.906	0.990	2.000	19.000	0.390
	Hotelling's Trace	0.104	0.990	2.000	19.000	0.390
	Roy's Largest Root	0.104	0.990	2.000	19.000	0.390
Ethnicity	Pillai's Trace	0.266	0.768	8.000	40.000	0.633
	Wilks' Lambda	0.736	0.788	8.000	38.000	0.616
	Hotelling's Trace	0.357	0.803	8.000	36.000	0.604
	Roy's Largest Root	0.350	1.750	4.000	20.000	0.179
Diagnosis	Pillai's Trace	0.149	0.536	6.000	40.000	0.777
	Wilks' Lambda	0.855	0.516	6.000	38.000	0.793
	Hotelling's Trace	0.165	0.495	6.000	36.000	0.808
	Roy's Largest Root	0.129	0.859	3.000	20.000	0.478
Number of antipsychotics pre-clozapine	Pillai's Trace	0.357	1.446	6.000	40.000	0.221
	Wilks' Lambda	0.674	1.381	6.000	38.000	0.247
	Hotelling's Trace	0.438	1.315	6.000	36.000	0.275
	Roy's Largest Root	0.272	1.815	3.000	20.000	0.177
Clozapine continuer or discontinuer	Pillai's Trace	0.224	2.750	2.000	19.000	0.089
	Wilks' Lambda	0.776	2.750	2.000	19.000	0.089
	Hotelling's Trace	0.289	2.750	2.000	19.000	0.089
	Roy's Largest Root	0.289	2.750	2.000	19.000	0.089

Table 7-202 MANOVA Levene's test of equality of error variances, age variable combined, intent to treat group

	F	df1	df2	Sig.
Net change in days of admission per year	2.432	81	20	0.014
Net change in number of admissions per year	1.536	81	20	0.139

Table 7-203 ANOVA summary table, age variable combined, intent to treat group

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	Net change in days of per year	291115.477	81	3594.018	1.746	0.079
	Net change in number of admissions per year	36.769	81	0.454	1.593	0.119
Intercept	Net change in days of per year	1907.653	1	1907.653	0.927	0.347
	Net change in number of	3.200	1	3.200	11.230	0.003

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
	admissions per year					
Age	Net change in days of per year	30949.841	3	10316.614	5.013	0.009
	Net change in number of admissions per year	2.260	3	0.753	2.644	0.077
Gender	Net change in days of per year	4186.576	1	4186.576	2.034	0.169
	Net change in number of admissions per year	0.172	1	0.172	0.603	0.447
Ethnicity	Net change in days of per year	2014.601	4	503.650	0.245	0.909
	Net change in number of admissions per year	0.472	4	0.118	0.414	0.796
Diagnosis	Net change in days of per year post-clozapine) per year	5231.681	3	1743.894	0.847	0.484
	Net change in number of admissions per year	0.367	3	0.122	0.430	0.734
Total number of antipsychotics pre-clozapine	Net change in days of per year	7428.049	3	2476.016	1.203	0.334
	Net change in number of admissions per year	1.480	3	0.493	1.732	0.193
Clozapine continuer or discontinuer	Net change in days of per year	11348.115	1	11348.115	5.514	0.029
	Net change in number of admissions per year	1.082	1	1.082	3.796	0.066
Error	Net change in days of per year	41161.853	20	2058.093		
	Net change in number of admissions per year	5.699	20	0.285		
Total	Net change in days of per year	360850.836	102			
	Net change in number of admissions per year	54.457	102			
Corrected Total	Net change in days of per year	332277.329	101			
	Net change in number of admissions per year	42.468	101			

Table 7-204 MANOVA eigenvalues, age variable combined, intent to treat group

Function	Eigenvalue	% of Variance	Cumulative %	Canonical Correlation
1	0.046	99.6	99.6	0.210
2	<0.0005	0.4	100.0	0.013

Table 7-205 MANOVA, significance tests for variates, age variable combined, intent to treat group

Test of Function(s)	Wilks' Lambda	Chi-square	df	Sig.
1 through 2	0.956	4.446	6	0.617
2	1.000	0.017	2	0.992

Table 7-206 MANOVA, canonical variate correlation coefficients, age variable combined, intent to treat group

	Function	
	1	2
Net change in days of admission per year	0.969	0.246
Net change in number of admissions per year	0.393	0.919

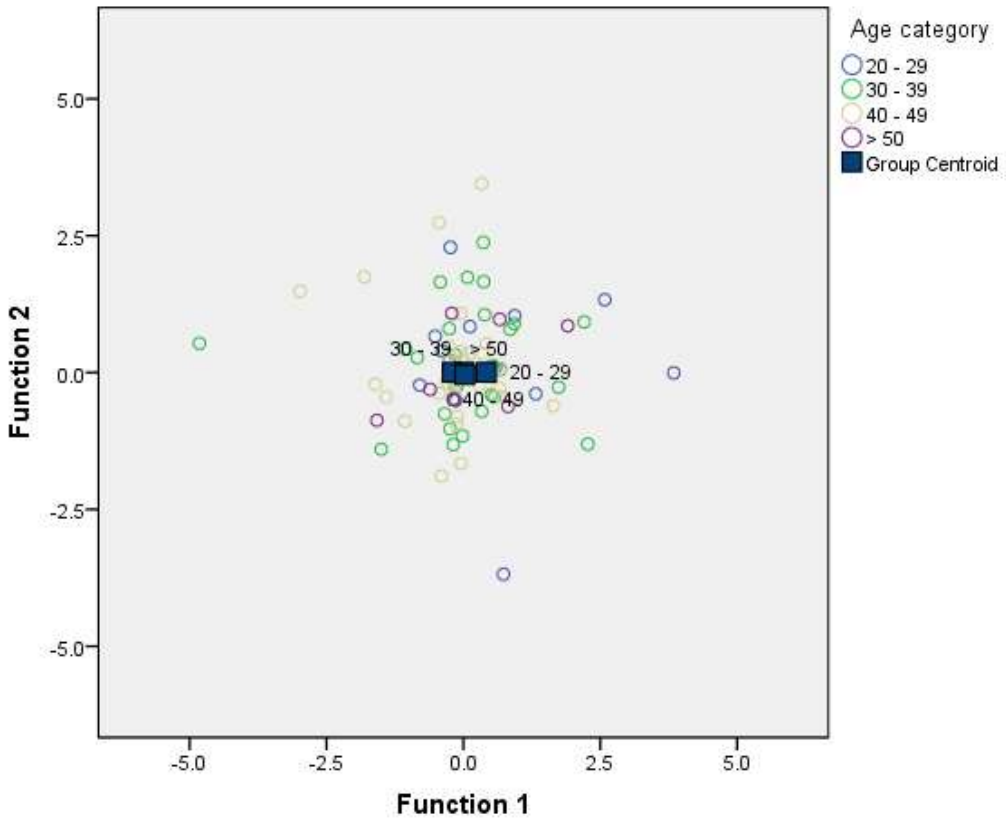


Figure 7-46 MANOVA, combined group plot, age variable combined, intent to treat group

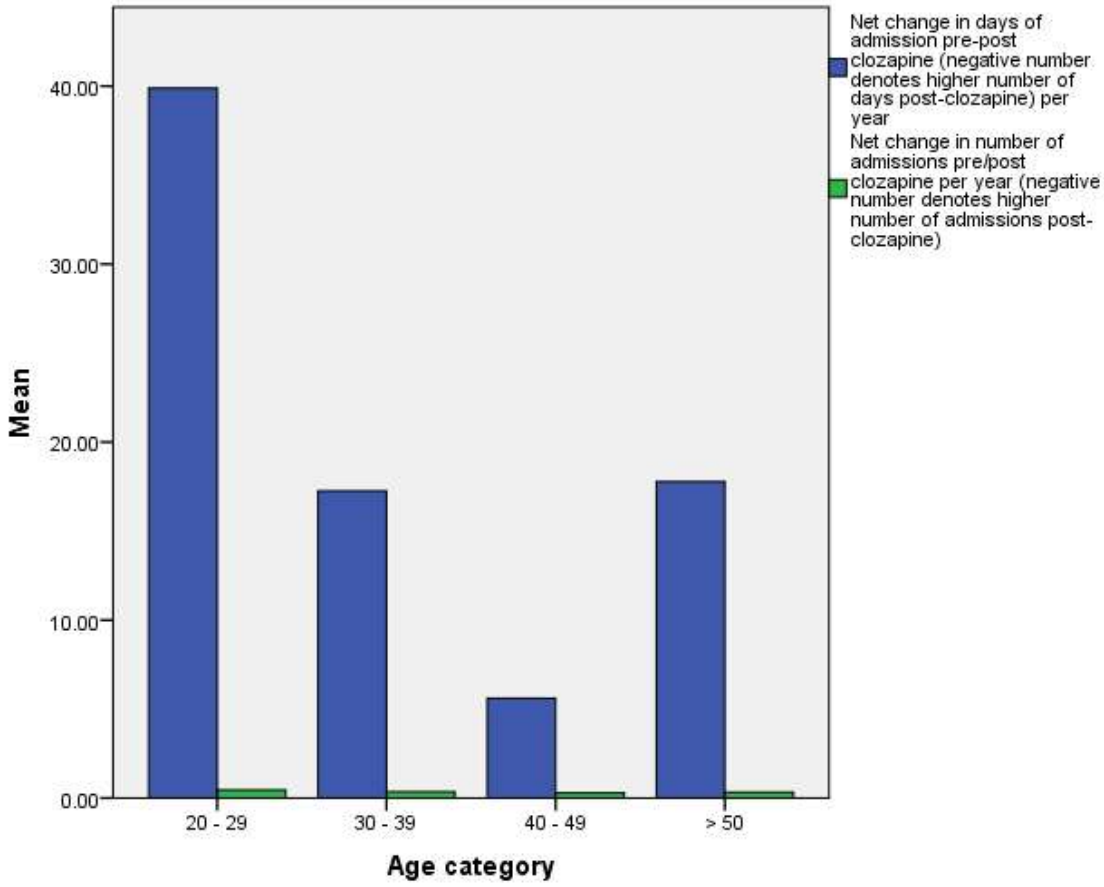


Figure 7-47 MANOVA histogram, age variable combined, intent to treat group

Table 7-207 MANOVA patient demographics, age outliers removed, intent to treat group

		Value Label	***N***
Age category	1	20 - 29	17
	2	30 - 39	37
	3	40 - 49	38
	4	50 - 59	8
Gender	1	Male	63
	2	Female	37
Ethnicity category	1	White	44
	2	Black	37
	3	Asian	9
	4	Mixed	7
	5	Other	3
Diagnosis	1	F20	66
	2	F25	17
	3	F31	6
	4	Other	11
Total number of antipsychotics pre-clozapine	1	1 - 2	15
	2	3 - 5	48
	3	6 - 10	27
	4	11 +	10
Clozapine continuer or discontinuer	0	Continuer	65
	1	Discontinuer	35

Table 7-208 MANOVA test for equality of covariance matrices, age outliers removed, intent to treat group

Box's M	16.046
F	1.087
df1	9
df2	686.575
Sig.	.370

Table 7-209 MANOVA test statistics, age outliers removed, intent to treat group

Effect		Value	F	Hypothesis df	Error df	Sig.
Intercept	Pillai's Trace	0.422	6.934	2.000	19.000	0.005
	Wilks' Lambda	0.578	6.934	2.000	19.000	0.005
	Hotelling's Trace	0.730	6.934	2.000	19.000	0.005
	Roy's Largest Root	0.730	6.934	2.000	19.000	0.005
Age	Pillai's Trace	0.601	2.866	6.000	40.000	0.020
	Wilks' Lambda	0.480	2.810	6.000	38.000	0.023
	Hotelling's Trace	0.915	2.745	6.000	36.000	0.027
	Roy's Largest Root	0.658	4.388	3.000	20.000	0.016
Gender	Pillai's Trace	0.065	0.659	2.000	19.000	0.529
	Wilks' Lambda	0.935	0.659	2.000	19.000	0.529
	Hotelling's Trace	0.069	0.659	2.000	19.000	0.529
	Roy's Largest Root	0.069	0.659	2.000	19.000	0.529
Ethnicity	Pillai's Trace	0.266	0.768	8.000	40.000	0.633
	Wilks' Lambda	0.736	0.788	8.000	38.000	0.616
	Hotelling's Trace	0.357	0.803	8.000	36.000	0.604
	Roy's Largest Root	0.350	1.750	4.000	20.000	0.179
Diagnosis	Pillai's Trace	0.149	0.536	6.000	40.000	0.777
	Wilks' Lambda	0.855	0.516	6.000	38.000	0.793
	Hotelling's Trace	0.165	0.495	6.000	36.000	0.808
	Roy's Largest Root	0.129	0.859	3.000	20.000	0.478
Number of antipsychotics pre-clozapine	Pillai's Trace	0.357	1.446	6.000	40.000	0.221
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	Hotelling's Trace	0.438	1.315	6.000	36.000	0.275
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Clozapine continuer or discontinuer	Pillai's Trace	0.224	2.750	2.000	19.000	0.089
	Wilks' Lambda	0.776	2.750	2.000	19.000	0.089
	Hotelling's Trace	0.289	2.750	2.000	19.000	0.089
	Roy's Largest Root	0.289	2.750	2.000	19.000	0.089

Table 7-210 MANOVA Levene's test of equality of error variances, age outliers removed, intent to treat group

	F	df1	df2	Sig.
Net change in days of admission per year	2.482	79	20	0.012
Net change in number of admissions per year	1.568	79	20	0.128

Table 7-211 ANOVA test results, age outliers removed, intent to treat group

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	Net change in days of admission per year	275805.019	79	3491.203	1.696	0.091
	Net change in number of admissions per year	35.721	79	0.452	1.587	0.122
Intercept	Net change in days of admission per year	1053.818	1	1053.818	0.512	0.483
	Net change in number of admissions per year	3.076	1	3.076	10.796	0.004
Age	Net change in days of admission per year	26783.170	3	8927.723	4.338	0.016
	Net change in number of admissions per year	2.779	3	0.926	3.251	0.043
Gender	Net change in days of admission per year	2853.128	1	2853.128	1.386	0.253
	Net change in number of admissions per year	0.182	1	0.182	0.639	0.433
Ethnicity	Net change in days of admission per year	2014.601	4	503.650	0.245	0.909
	Net change in number of admissions per year	0.472	4	0.118	0.414	0.796
Diagnosis	Net change in days of admission per year	5231.681	3	1743.894	0.847	0.484
	Net change in number of admissions per year	0.367	3	0.122	0.430	0.734
Number of antipsychotics pre-clozapine	Net change in days of admission per year	7428.049	3	2476.016	1.203	0.334
	Net change in number of admissions per year	1.480	3	0.493	1.732	0.193
Clozapine continuer or discontinuer	Net change in days of admission per year	11348.115	1	11348.115	5.514	0.029
	Net change in number of admissions per year	1.082	1	1.082	3.796	0.066

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Error	Net change in days of admission per year	41161.853	20	2058.093		
	Net change in number of admissions per year	5.699	20	0.285		
Total	Net change in days of admission per year	340073.608	100			
	Net change in number of admissions per year	52.602	100			
Corrected Total	Net change in days of admission per year	316966.872	99			
	Net change in number of admissions per year	41.420	99			

Table 7-212 MANOVA eigenvalues, age outliers removed, intent to treat group

Eigenvalue	% of Variance	Cumulative %	Canonical Correlation
0.056	99.2	99.2	0.230
0.000	0.8	100.0	0.021

Table 7-213 MANOVA, significance tests for variates, age outliers removed, intent to treat group

Test of Function(s)	Wilks' Lambda	Chi-square	df	Sig.
1 through 2	0.947	5.271	6	0.510
2	1.000	0.042	2	0.979

Table 7-214 MANOVA, canonical variate correlation coefficients, age outliers removed, intent to treat group

	Function	
	1	2
Net change in days of admission per year	0.979	0.202
Net change in number of admissions per year	0.422	0.907

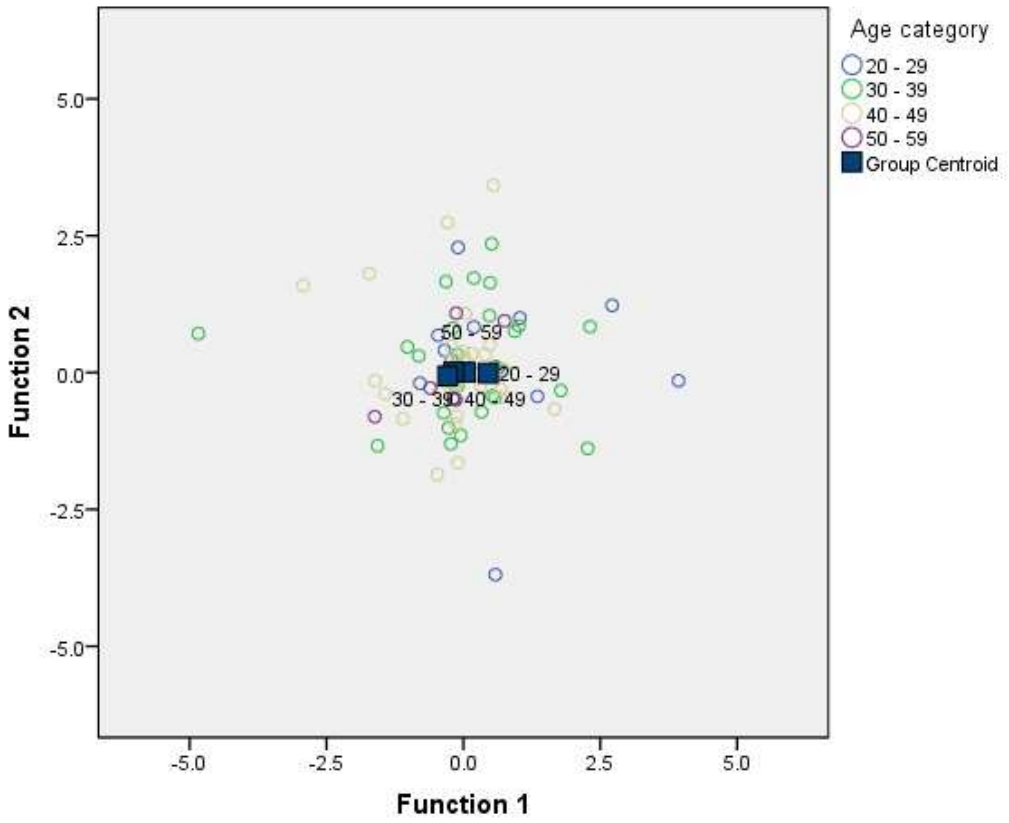

Figure 7-48 MANOVA, combined group plot, age outliers removed, intent to treat group

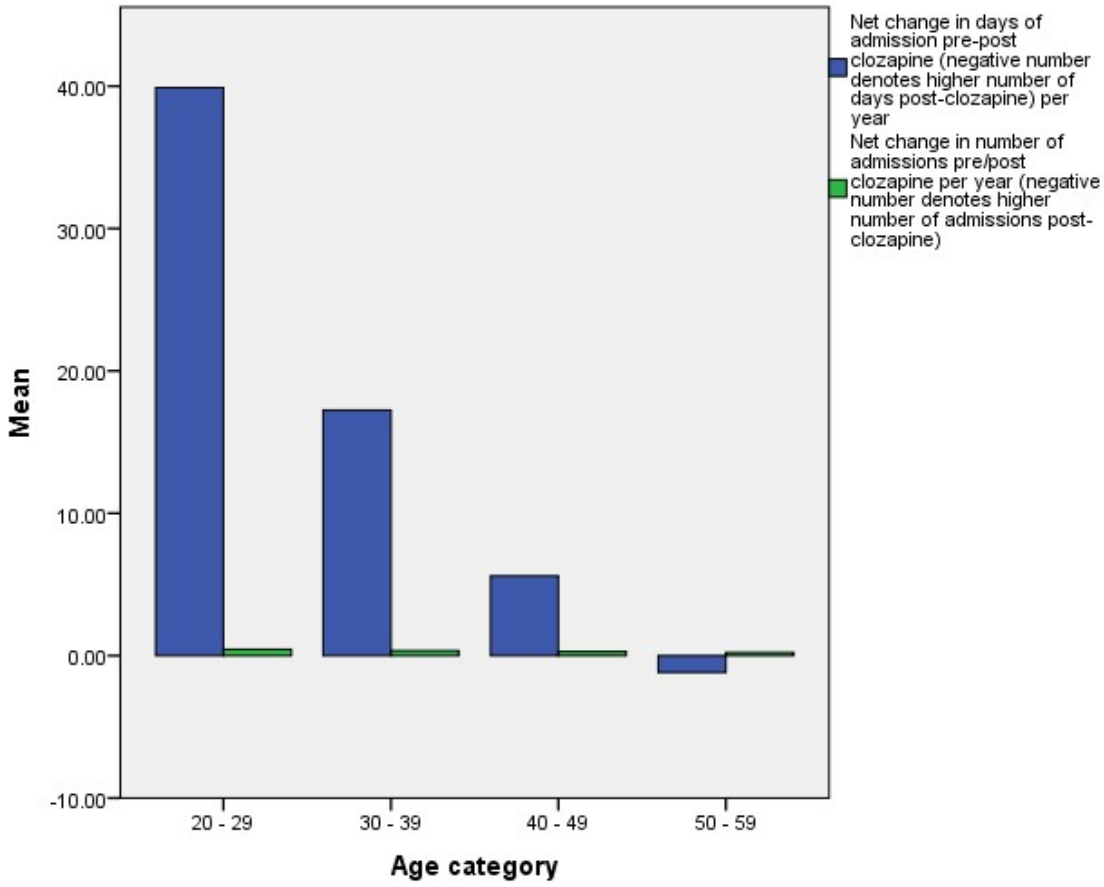

Figure 7-49 MANOVA histogram, age outliers removed, intent to treat group

Table 7-215 MANOVA patient demographics, clozapine continuers group

		Value Label	***N***
Age category	1	20 - 29	9
	2	30 - 39	23
	3	40 - 49	28
	4	50 - 59	5
Ethnicity category	1	White	29
	2	Black	23
	3	Other	13
Gender	1	Male	36
	2	Female	29
Diagnosis	1	F20	41
	2	F25	12
	3	Other	12
Total number of antipsychotics pre-clozapine	1	1 - 2	12
	2	3 - 5	27
	3	6 - 10	17
	4	11 +	9

Table 7-216 MANOVA test for equality of covariance matrices, clozapine continuers group

Box's M	2.702
F	0.486
df1	3
df2	1030.389
Sig.	0.692

Table 7-217 MANOVA test statistics, clozapine continuers group

Effect		Value	F	Hypothesis df	Error df	Sig.
Intercept	Pillai's Trace	0.746	17.639	2.000	12.000	<0.0005
	Wilks' Lambda	0.254	17.639	2.000	12.000	<0.0005
	Hotelling's Trace	2.940	17.639	2.000	12.000	<0.0005
	Roy's Largest Root	2.940	17.639	2.000	12.000	<0.0005
Age	Pillai's Trace	0.689	2.276	6.000	26.000	0.067
	Wilks' Lambda	0.414	2.216	6.000	24.000	0.077
	Hotelling's Trace	1.166	2.138	6.000	22.000	0.089
	Roy's Largest Root	0.886	3.838	3.000	13.000	0.036
Ethnicity	Pillai's Trace	0.370	1.475	4.000	26.000	0.238
	Wilks' Lambda	0.636	1.523	4.000	24.000	0.227
	Hotelling's Trace	0.563	1.548	4.000	22.000	0.223
	Roy's Largest Root	0.546	3.546	2.000	13.000	0.059
Gender	Pillai's Trace	0.213	1.628	2.000	12.000	0.237
	Wilks' Lambda	0.787	1.628	2.000	12.000	0.237
	Hotelling's Trace	0.271	1.628	2.000	12.000	0.237
	Roy's Largest Root	0.271	1.628	2.000	12.000	0.237
Diagnosis	Pillai's Trace	0.111	0.383	4.000	26.000	0.819
	Wilks' Lambda	0.889	0.362	4.000	24.000	0.833
	Hotelling's Trace	0.123	0.340	4.000	22.000	0.848
	Roy's Largest Root	0.117	0.759	2.000	13.000	0.488
Number of antipsychotics pre-clozapine	Pillai's Trace	0.579	1.767	6.000	26.000	0.145
	Wilks' Lambda	0.501	1.650	6.000	24.000	0.177
	Hotelling's Trace	0.835	1.530	6.000	22.000	0.215
	Roy's Largest Root	0.535	2.317	3.000	13.000	0.123

Table 7-218 MANOVA Levene's test of equality of error variances, clozapine continuers group

	F	df1	df2	Sig.
Net change in days of admission per year	7.419	51	13	<0.0005
Net change in number of admissions per year	1.608	51	13	0.175

Table 7-219 ANOVA test results, clozapine continuers group

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	Net change in days of admission per year	115377.498	51	2262.304	1.400	0.259
	Net change in number of admissions per year	15.843	51	0.311	1.872	0.108
Intercept	Net change in days of admission per year	23348.243	1	23348.243	14.451	0.002
	Net change in number of admissions per year	6.244	1	6.244	37.634	<0.0005
Age	Net change in days of admission per year	15939.674	3	5313.225	3.289	0.055
	Net change in number of admissions per year	1.546	3	0.515	3.106	0.064
Ethnicity	Net change in days of admission per year	542.458	2	271.229	0.168	0.847
	Net change in number of admissions per year	0.742	2	0.371	2.236	0.146
Gender	Net change in days of admission per year	151.311	1	151.311	0.094	0.764
	Net change in number of admissions per year	0.507	1	0.507	3.055	0.104
Diagnosis	Net change in days of admission per year	529.911	2	264.955	0.164	0.850
	Net change in number of admissions per year	0.092	2	0.046	0.278	0.762
Number of antipsychotics pre-clozapine	Net change in days of admission per year	7125.819	3	2375.273	1.470	0.268
	Net change in number of admissions per year	1.146	3	0.382	2.303	0.125

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Error	Net change in days of admission per year	21003.425	13	1615.648		
	Net change in number of admissions per year	2.157	13	0.166		
Total	Net change in days of admission per year	169639.109	65			
	Net change in number of admissions per year	27.287	65			
Corrected Total	Net change in days of admission per year	136380.923	64			
	Net change in number of admissions per year	18.000	64			

Table 7-220 MANOVA eigenvalues, clozapine continuers group

Function	Eigenvalue	% of Variance	Cumulative %	Canonical Correlation
1	0.059	92.2	92.2	0.237
2	0.005	7.8	100.0	0.070

Table 7-221 MANOVA, significance tests for variates, clozapine continuers group

Test of Function(s)	Wilks' Lambda	Chi-square	df	Sig.
1 through 2	0.939	3.817	6	0.701
2	0.995	0.304	2	0.859

Table 7-222 MANOVA, canonical variate correlation coefficients, clozapine continuers group

	Function	
	1	2
Net change in days of admission per year	0.968	0.249
Net change in number of admissions per year	0.372	0.928

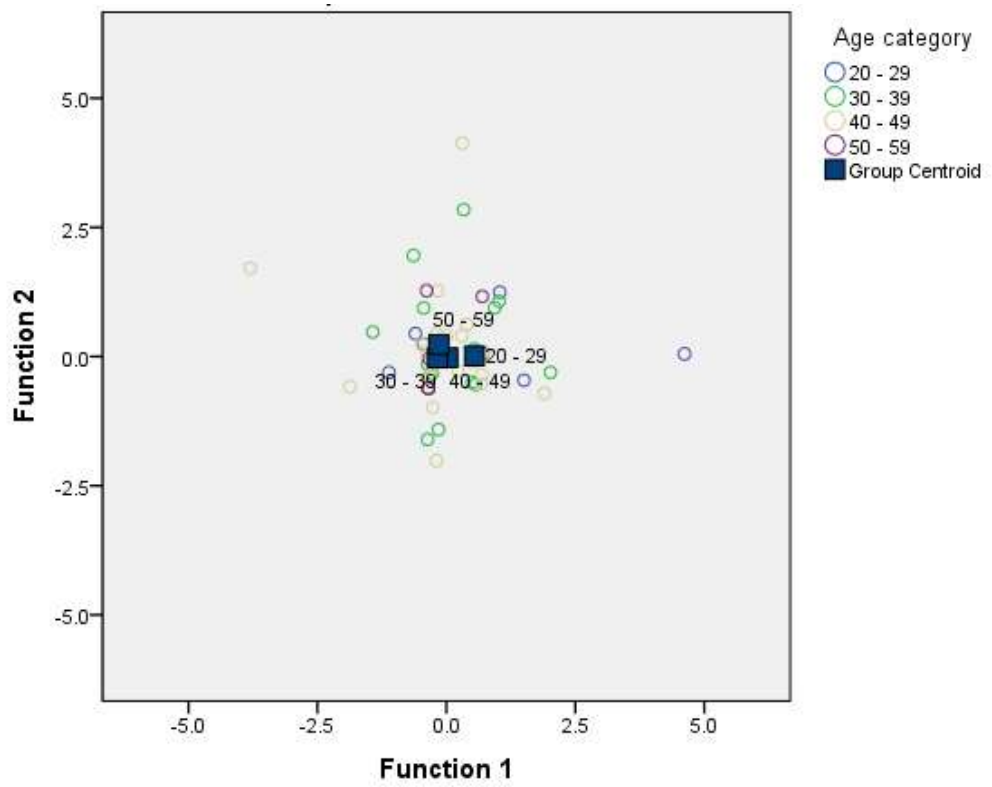

Figure 7-50 MANOVA combined groups plot, age variable, clozapine continuers group

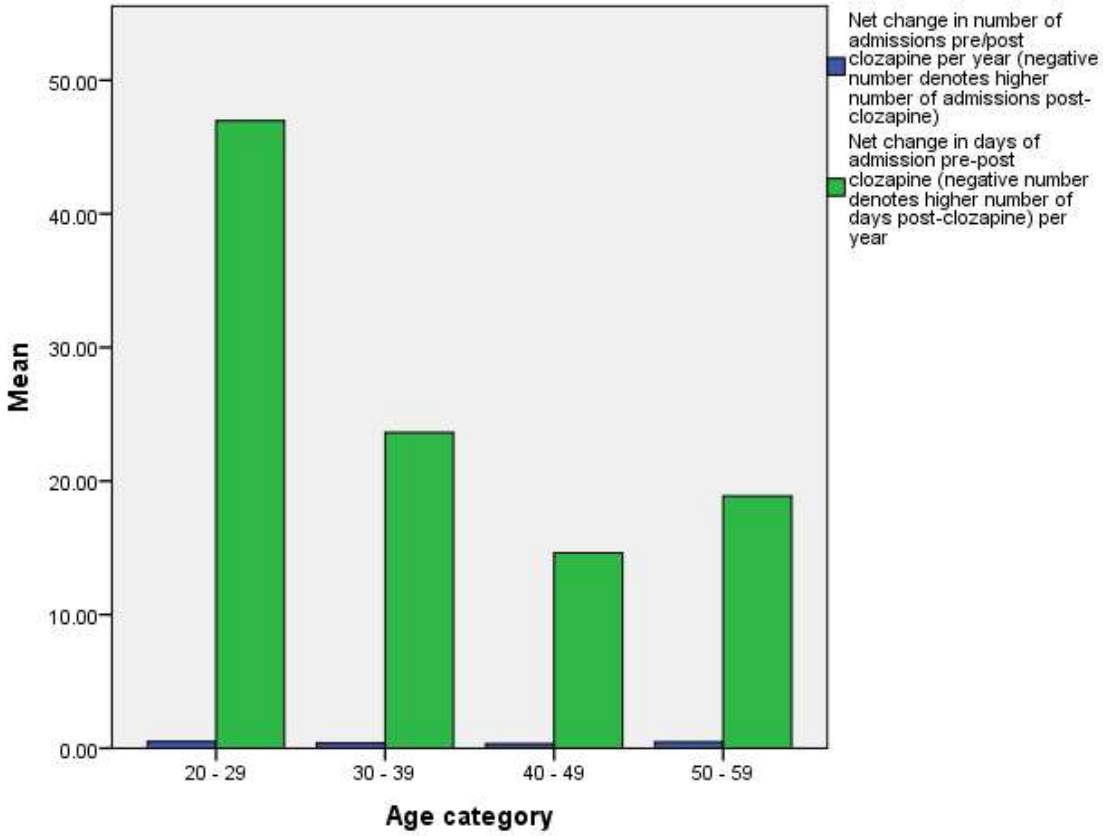

Figure 7-51 MANOVA histogram, age variable. clozapine continuers group

Table 7-223 MANOVA patient demographics, clozapine discontinuers group

		Value Label	*N*
Age	1	20 - 29	8
	2	30 - 39	14
	3	40 - 49	10
	4	50 - 59	3
Ethnicity	1	White	15
	2	Black	14
	3	Other	6
Gender	1	Male	27
	2	Female	8
Diagnosis	1	F20	25
	2	F25	5
	3	Other	5
Total number of antipsychotics pre-clozapine category	1	1 - 2	3
	2	3 - 5	21
	3	6 - 10	10
	4	11 +	1

Table 7-224 MANOVA test for equality of covariance matrices, clozapine discontinuers group

Box's M	8.349
F	1.502
df1	3
df2	1030.389
Sig.	0.212

Table 7-225 MANOVA test statistics, clozapine discontinuers group

Effect		Value	F	Hypothesis df	Error df	Sig.
Intercept	Pillai's Trace	0.446	2.816	2.000	7.000	0.127
	Wilks' Lambda	0.554	2.816	2.000	7.000	0.127
	Hotelling's Trace	0.804	2.816	2.000	7.000	0.127
	Roy's Largest Root	0.804	2.816	2.000	7.000	0.127
Age	Pillai's Trace	0.203	0.452	4.000	16.000	0.770
	Wilks' Lambda	0.797	0.421	4.000	14.000	0.791
	Hotelling's Trace	0.255	0.382	4.000	12.000	0.817
	Roy's Largest Root	0.255	1.018	2.000	8.000	0.404
Ethnicity	Pillai's Trace	0.290	0.677	4.000	16.000	0.618
	Wilks' Lambda	0.716	0.638	4.000	14.000	0.644
	Hotelling's Trace	0.390	0.586	4.000	12.000	0.679
	Roy's Largest Root	0.371	1.484	2.000	8.000	0.283
Gender	Pillai's Trace	0.595	5.145	2.000	7.000	0.042
	Wilks' Lambda	0.405	5.145	2.000	7.000	0.042
	Hotelling's Trace	1.470	5.145	2.000	7.000	0.042
	Roy's Largest Root	1.470	5.145	2.000	7.000	0.042
Diagnosis	Pillai's Trace	0.617	1.784	4.000	16.000	0.181
	Wilks' Lambda	0.410	1.965	4.000	14.000	0.155
	Hotelling's Trace	1.372	2.058	4.000	12.000	0.150
	Roy's Largest Root	1.322	5.289	2.000	8.000	0.034
Number of antipsychotics pre-clozapine	Pillai's Trace	0.265	0.610	4.000	16.000	0.661
	Wilks' Lambda	0.738	0.574	4.000	14.000	0.686
	Hotelling's Trace	0.351	0.527	4.000	12.000	0.718
	Roy's Largest Root	0.340	1.361	2.000	8.000	0.310

Table 7-226 MANOVA Levene's test of equality of error variances, clozapine discontinuers group

	F	df1	df2	Sig.
Net change in days of admission per year	1.706	26	8	0.220
Net change in number of admissions per year	1.844	26	8	0.186

Table 7-227 ANOVA test statistics, clozapine discontinuers group

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	Net change in days of admission per year	149587.832	26	5753.378	2.215	0.122
	Net change in number of admissions per year	19.287	26	0.742	1.570	0.260
Intercept	Net change in days of admission per year	5258.478	1	5258.478	2.025	0.193
	Net change in number of admissions per year	0.101	1	0.101	0.213	0.657
Age	Net change in days of admission per year	3044.689	2	1522.344	0.586	0.579
	Net change in number of admissions per year	0.958	2	0.479	1.014	0.405
Ethnicity	Net change in days of admission per year	3683.176	2	1841.588	0.709	0.521
	Net change in number of admissions per year	0.076	2	0.038	0.080	0.924
Gender	Net change in days of admission per year	15546.102	1	15546.102	5.986	0.040
	Net change in number of admissions per year	5.557	1	5.557	11.760	0.009
Diagnosis	Net change in days of admission per year	27296.754	2	13648.377	5.255	0.035
	Net change in number of admissions per year	2.238	2	1.119	2.368	0.156
Number of antipsychotics pre-clozapine	Net change in days of admission per year	1620.352	2	810.176	0.312	0.741
	Net change in number of admissions per year	0.157	2	0.079	0.166	0.850
Error	Net change in days of admission per year	20775.837	8	2596.980		
	Net change in number of admissions per year	3.780	8	0.472		

Source	Dependent Variable	Type III Sum of Squares	df	Mean Square	F	Sig.
Total	Net change in days of admission per year	170434.499	35			
	Net change in number of admissions per year	25.315	35			
Corrected Total	Net change in days of admission per year	170363.669	34			
	Net change in number of admissions per year	23.067	34			

Table 7-228 MANOVA eigenvalues, clozapine discontinuers group

Function	Eigenvalue	% of Variance	Cumulative %	Canonical Correlation
1	0.105	88.0	88.0	0.309
2	0.014	12.0	100.0	0.119

Table 7-229 MANOVA, significance tests for variates, clozapine discontinuers group

Test of Function(s)	Wilks' Lambda	Chi-square	df	Sig.
1 through 2	0.892	3.542	6	0.738
2	0.986	0.442	2	0.802

Table 7-230 MANOVA, canonical variate correlation coefficients, clozapine discontinuers group

	Function	
	1	2
Net change in days of admission per year	0.998	0.065
Net change in number of admissions per year	0.531	0.847

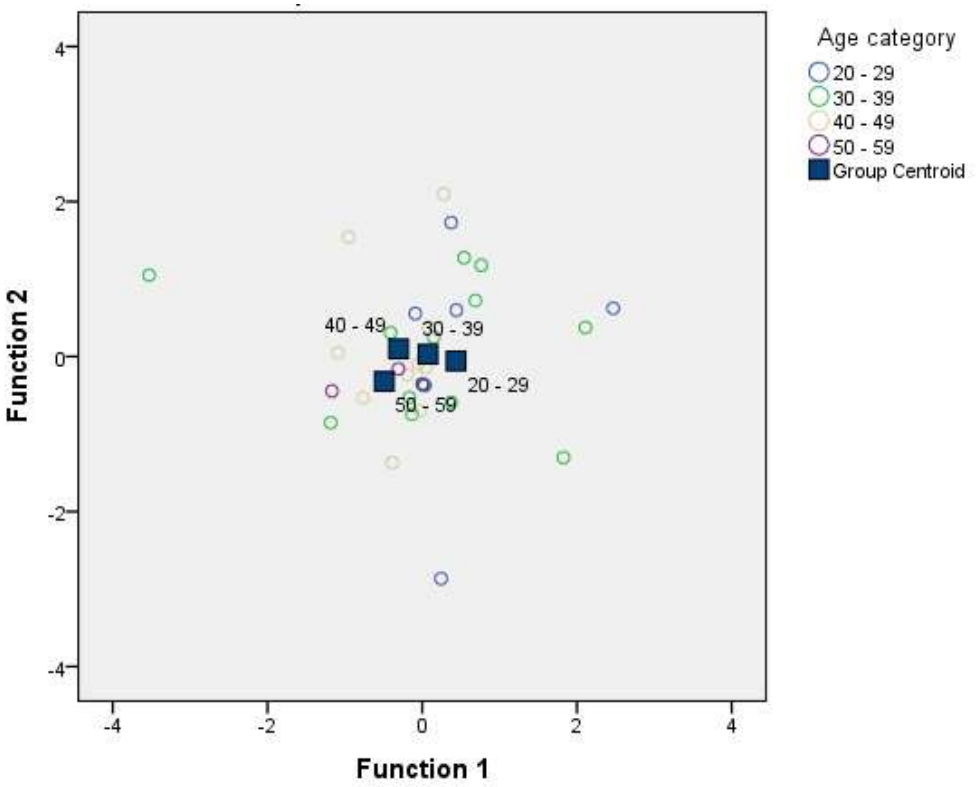

Figure 7-52 MANOVA combined groups plot, age variable, clozapine discontinuers group

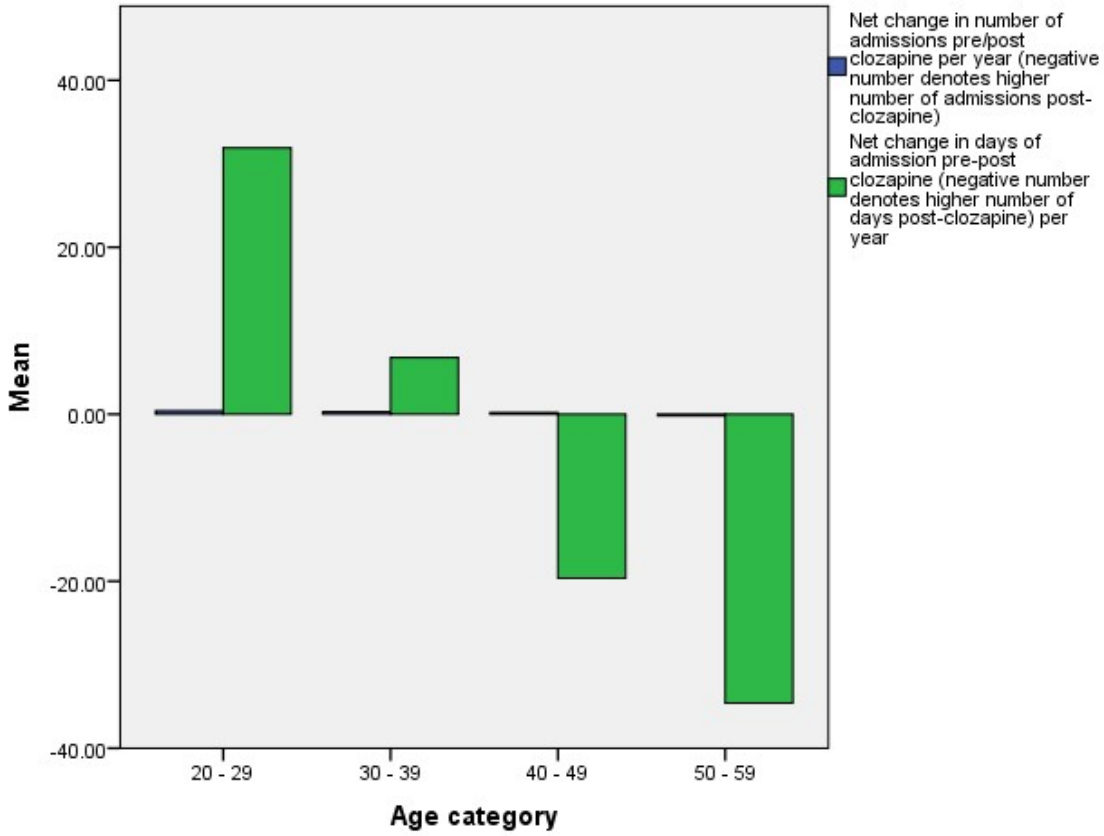

Figure 7-53 MANOVA histogram, age variable, clozapine discontinuers group

Table 7-231 MANOVA, eigenvalues, gender variable, clozapine discontinuers group

Function	Eigenvalue	% of Variance	Cumulative %	Canonical Correlation
1	0.042	100.0	100.0	0.201

Table 7-232 MANOVA, significance tests for variates, gender variable, clozapine discontinuers group

Test of Function(s)	Wilks' Lambda	Chi-square	df	Sig.
1	0.960	1.318	2	0.517

Table 7-233 MANOVA, canonical variate correlation coefficients, gender variable, clozapine discontinuers group

	Function
	1
Net change in number of admissions per year	0.979
Net change in days of admission per year	0.418

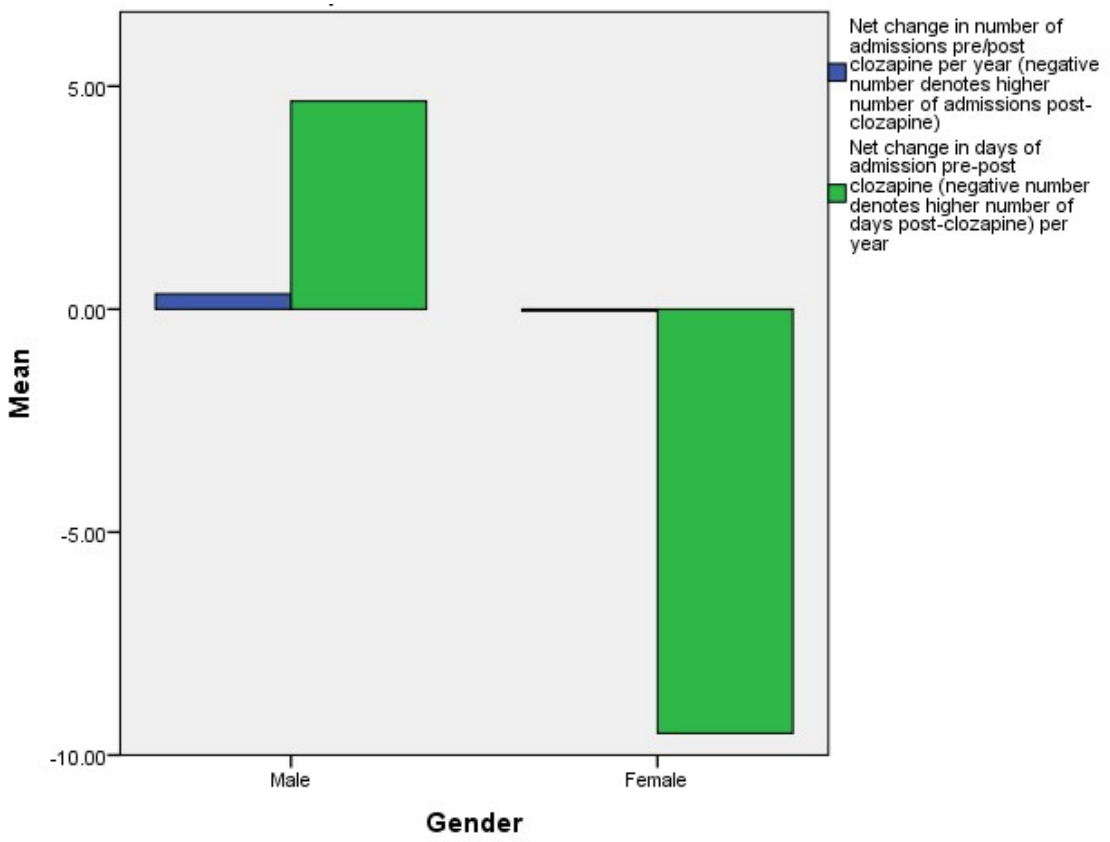

Figure 7-54 MANOVA histogram, gender variable, clozapine discontinuers group

Table 7-234 MANOVA, eigenvalues, diagnosis variable, clozapine discontinuers group

Function	Eigenvalue	% of Variance	Cumulative %	Canonical Correlation
1	0.090	72.2	72.2	0.287
2	0.035	27.8	100.0	0.183

Table 7-235 MANOVA, significance tests for variates, diagnosis variable, clozapine discontinuers group

Test of Function(s)	Wilks' Lambda	Chi-square	df	Sig.
1 through 2	0.887	3.783	4	0.436
2	0.967	1.072	1	0.301

Table 7-236 MANOVA, canonical variate correlation coefficients, diagnosis variable, clozapine discontinuers group

	Function	
	1	2
Net change in number of admissions per year	0.999	0.043
Net change in days of admission per year	0.554	0.832

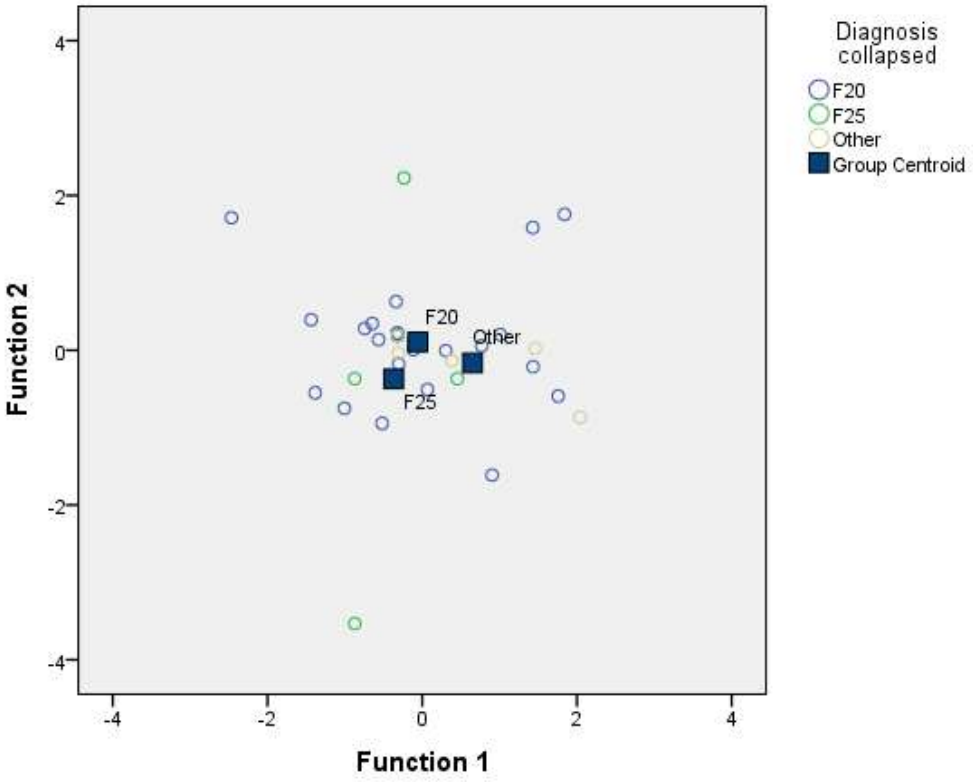

Figure 7-55 MANOVA, combined groups plot, diagnosis variable, clozapine discontinuers group

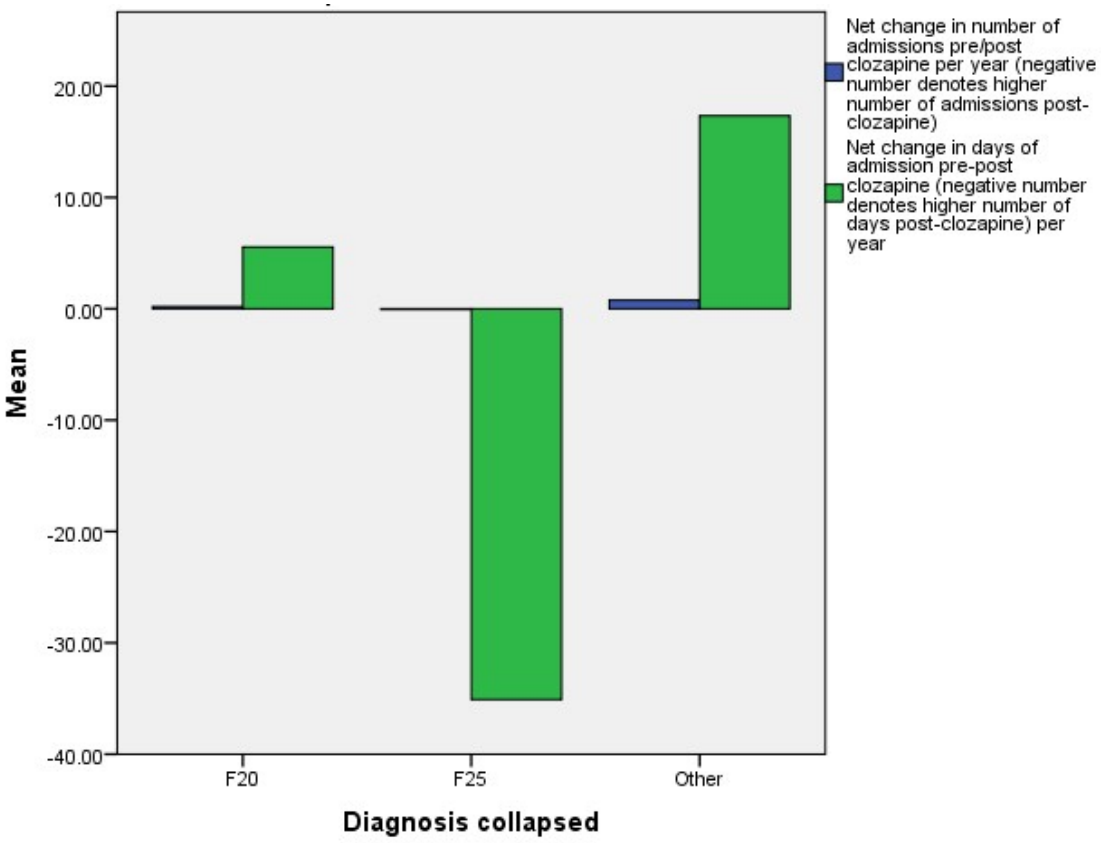

Figure 7-56 MANOVA, histogram, diagnosis variable, clozapine discontinuers group

Appendix H. Statistical data for chapter 6

Table 7-237 t-test, continuous variables

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	T	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Age	Equal variances assumed	0.040	0.842	1.811	131	0.072	3.246	1.793	-0.300	6.792
	Equal variances not assumed			1.827	100.362	0.071	3.246	1.776	-0.278	6.769
Gender	Equal variances assumed	35.324	<0.0005	2.578	131	0.011	0.210	0.081	0.049	0.371
	Equal variances not assumed			2.767	118.587	0.007	0.210	0.076	0.060	0.360
Clozapine theoretical delay	Equal variances assumed	0.055	0.814	0.332	131	0.741	0.264	0.797	-1.312	1.841
	Equal variances not assumed			0.328	94.189	0.744	0.264	0.807	-1.337	1.866
Total number of antipsychotics pre-clozapine	Equal variances assumed	1.519	0.220	0.237	131	0.813	0.162	0.685	-1.194	1.519
	Equal variances not assumed			0.254	118.082	0.800	0.162	0.640	-1.104	1.429

Table 7-238 Chi-square test, ethnicity

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Pearson Chi-Square	4.615	4	0.329	0.335		
Likelihood Ratio	5.230	4	0.265	0.318		
Fisher's Exact Test	4.758			0.298		
Linear-by-Linear Association	0.274	1	0.601	0.650	0.337	0.064
N of Valid Cases	133					

Table 7-239 Chi-square test, diagnosis

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Pearson Chi-Square	0.012	2	0.994	1.000		
Likelihood Ratio	0.012	2	0.994	1.000		
Fisher's Exact Test	0.059			1.000		
Linear-by-Linear Association	0.001	1	0.982	1.000	0.542	0.094
N of Valid Cases	133					

Table 7-240 Multiway crosstabulation table, gender x clozapine continuer or discontinuer x ethnicity

Ethnicity				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
White	Gender	Male	Count	2_a	3_a	5
			Expected Count	2.1	2.9	5.0
			% within Gender	40.0%	60.0%	100.0%
			% within clozapine continuer or discontinuer	66.7%	75.0%	71.4%
			% of Total	28.6%	42.9%	71.4%
			Std. Residual	-0.1	0.1	
		Female	Count	1_a	1_a	2
			Expected Count	0.9	1.1	2.0
			% within Gender	50.0%	50.0%	100.0%
			% within clozapine continuer or discontinuer	33.3%	25.0%	28.6%
			% of Total	14.3%	14.3%	28.6%
			Std. Residual	0.2	-0.1	
	Total		Count	3	4	7
			Expected Count	3.0	4.0	7.0
			% within Gender	42.9%	57.1%	100.0%
			% within clozapine	100.0%	100.0%	100.0%

Ethnicity				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			continuer or discontinuer			
			% of Total	42.9%	57.1%	100.0%
Black British	Gender	Male	Count	2[a]	3[a]	5
			Expected Count	2.2	2.8	5.0
			% within Gender	40.0%	60.0%	100.0%
			% within clozapine continuer or discontinuer	50.0%	60.0%	55.6%
			% of Total	22.2%	33.3%	55.6%
			Std. Residual	-0.1	0.1	
		Female	Count	2[a]	2[a]	4
			Expected Count	1.8	2.2	4.0
			% within Gender	50.0%	50.0%	100.0%
			% within clozapine continuer or discontinuer	50.0%	40.0%	44.4%
			% of Total	22.2%	22.2%	44.4%
			Std. Residual	0.2	-0.1	
	Total		Count	4	5	9
			Expected Count	4.0	5.0	9.0
			% within Gender	44.4%	55.6%	100.0%
			% within clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	44.4%	55.6%	100.0%
Black African	Gender	Male	Count	9[a]	2[a]	11
			Expected Count	9.7	1.3	11.0
			% within Gender	81.8%	18.2%	100.0%
			% within clozapine continuer or discontinuer	60.0%	100.0%	64.7%
			% of Total	52.9%	11.8%	64.7%
			Std. Residual	-0.2	0.6	
		Female	Count	6[a]	0[a]	6
			Expected Count	5.3	0.7	6.0
			% within Gender	100.0%	0.0%	100.0%
			% within clozapine	40.0%	0.0%	35.3%

Ethnicity				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			continuer or discontinuer			
			% of Total	35.3%	0.0%	35.3%
			Std. Residual	0.3	-0.8	
	Total		Count	15	2	17
			Expected Count	15.0	2.0	17.0
			% within Gender	88.2%	11.8%	100.0%
			% within clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	88.2%	11.8%	100.0%
Caribbean	Gender	Male	Count	3[a]	12[a]	15
			Expected Count	4.5	10.5	15.0
			% within Gender	20.0%	80.0%	100.0%
			% within clozapine continuer or discontinuer	50.0%	85.7%	75.0%
			% of Total	15.0%	60.0%	75.0%
			Std. Residual	-0.7	0.5	
		Female	Count	3[a]	2[a]	5
			Expected Count	1.5	3.5	5.0
			% within Gender	60.0%	40.0%	100.0%
			% within clozapine continuer or discontinuer	50.0%	14.3%	25.0%
			% of Total	15.0%	10.0%	25.0%
			Std. Residual	1.2	-0.8	
	Total		Count	6	14	20
			Expected Count	6.0	14.0	20.0
			% within Gender	30.0%	70.0%	100.0%
			% within clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	30.0%	70.0%	100.0%
British	Gender	Male	Count	23[a]	11[a]	34
			Expected Count	25.1	8.9	34.0
			% within Gender	67.6%	32.4%	100.0%
			% within clozapine	67.6%	91.7%	73.9%

Ethnicity				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			continuer or discontinuer			
			% of Total	50.0%	23.9%	73.9%
			Std. Residual	-0.4	0.7	
		Female	Count	11[a]	1[a]	12
			Expected Count	8.9	3.1	12.0
			% within Gender	91.7%	8.3%	100.0%
			% within clozapine continuer or discontinuer	32.4%	8.3%	26.1%
			% of Total	23.9%	2.2%	26.1%
			Std. Residual	0.7	-1.2	
	Total		Count	34	12	46
			Expected Count	34.0	12.0	46.0
			% within Gender	73.9%	26.1%	100.0%
			% within clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	73.9%	26.1%	100.0%
Chinese	Gender	Male	Count		1	1
			Expected Count		1.0	1.0
			% within Gender		100.0%	100.0%
			% within clozapine continuer or discontinuer		50.0%	50.0%
			% of Total		50.0%	50.0%
			Std. Residual		0.0	
		Female	Count		1	1
			Expected Count		1.0	1.0
			% within Gender		100.0%	100.0%
			% within clozapine continuer or discontinuer		50.0%	50.0%
			% of Total		50.0%	50.0%
			Std. Residual		0.0	
	Total		Count		2	2
			Expected Count		2.0	2.0
			% within Gender		100.0%	100.0%
			% within clozapine		100.0%	100.0%

Ethnicity				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			continuer or discontinuer			
			% of Total		100.0%	100.0%
Iranian	Gender	Female	Count	1		1
			Expected Count	1.0		1.0
			% within Gender	100.0%		100.0%
			% within clozapine continuer or discontinuer	100.0%		100.0%
			% of Total	100.0%		100.0%
			Std. Residual	0.0		
	Total		Count	1		1
			Expected Count	1.0		1.0
			% within Gender	100.0%		100.0%
			% within clozapine continuer or discontinuer	100.0%		100.0%
			% of Total	100.0%		100.0%
Other African	Gender	Male	Count	4_a	1_a	5
			Expected Count	3.8	1.3	5.0
			% within Gender	80.0%	20.0%	100.0%
			% within clozapine continuer or discontinuer	66.7%	50.0%	62.5%
			% of Total	50.0%	12.5%	62.5%
			Std. Residual	0.1	-0.2	
		Female	Count	2_a	1_a	3
			Expected Count	2.3	.8	3.0
			% within Gender	66.7%	33.3%	100.0%
			% within clozapine continuer or discontinuer	33.3%	50.0%	37.5%
			% of Total	25.0%	12.5%	37.5%
			Std. Residual	-0.2	0.3	
	Total		Count	6	2	8
			Expected Count	6.0	2.0	8.0
			% within Gender	75.0%	25.0%	100.0%
			% within clozapine	100.0%	100.0%	100.0%

Ethnicity				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			continuer or discontinuer			
			% of Total	75.0%	25.0%	100.0%
Eritraen	Gender	Male	Count	0[a]	1[a]	1
			Expected Count	0.5	0.5	1.0
			% within Gender	0.0%	100.0%	100.0%
			% within clozapine continuer or discontinuer	0.0%	100.0%	50.0%
			% of Total	0.0%	50.0%	50.0%
			Std. Residual	-0.7	0.7	
		Female	Count	1[a]	0[a]	1
			Expected Count	.5	.5	1.0
			% within Gender	100.0%	0.0%	100.0%
			% within clozapine continuer or discontinuer	100.0%	0.0%	50.0%
			% of Total	50.0%	0.0%	50.0%
			Std. Residual	0.7	-0.7	
	Total		Count	1	1	2
			Expected Count	1.0	1.0	2.0
			% within Gender	50.0%	50.0%	100.0%
			% within clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	50.0%	50.0%	100.0%
Arab	Gender	Male	Count		1	1
			Expected Count		1.0	1.0
			% within Gender		100.0%	100.0%
			% within clozapine continuer or discontinuer		100.0%	100.0%
			% of Total		100.0%	100.0%
			Std. Residual		.0	
	Total		Count		1	1
			Expected Count		1.0	1.0
			% within Gender		100.0%	100.0%
			% within clozapine		100.0%	100.0%

Ethnicity				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			continuer or discontinuer			
			% of Total		100.0%	100.0%
Black and White Caribbean	Gender	Male	Count	7[a]	1[a]	8
			Expected Count	7.2	.8	8.0
			% within Gender	87.5%	12.5%	100.0%
			% within clozapine continuer or discontinuer	77.8%	100.0%	80.0%
			% of Total	70.0%	10.0%	80.0%
			Std. Residual	-0.1	0.2	
		Female	Count	2[a]	0[a]	2
			Expected Count	1.8	.2	2.0
			% within Gender	100.0%	0.0%	100.0%
			% within clozapine continuer or discontinuer	22.2%	0.0%	20.0%
			% of Total	20.0%	0.0%	20.0%
			Std. Residual	0.1	-0.4	
	Total		Count	9	1	10
			Expected Count	9.0	1.0	10.0
			% within Gender	90.0%	10.0%	100.0%
			% within clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	90.0%	10.0%	100.0%
Cypriot	Gender	Male	Count		1	1
			Expected Count		1.0	1.0
			% within Gender		100.0%	100.0%
			% within clozapine continuer or discontinuer		100.0%	100.0%
			% of Total		100.0%	100.0%
			Std. Residual		0.0	
	Total		Count		1	1
			Expected Count		1.0	1.0
			% within Gender		100.0%	100.0%
			% within clozapine		100.0%	100.0%

Ethnicity				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			continuer or discontinuer			
			% of Total		100.0%	100.0%
Indian	Gender	Male	Count	0_a	1_a	1
			Expected Count	0.7	0.3	1.0
			% within Gender	0.0%	100.0%	100.0%
			% within clozapine continuer or discontinuer	0.0%	100.0%	33.3%
			% of Total	0.0%	33.3%	33.3%
			Std. Residual	-0.8	1.2	
		Female	Count	2_a	0_a	2
			Expected Count	1.3	.7	2.0
			% within Gender	100.0%	0.0%	100.0%
			% within clozapine continuer or discontinuer	100.0%	0.0%	66.7%
			% of Total	66.7%	0.0%	66.7%
			Std. Residual	0.6	-0.8	
	Total		Count	2	1	3
			Expected Count	2.0	1.0	3.0
			% within Gender	66.7%	33.3%	100.0%
			% within clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	66.7%	33.3%	100.0%
Pakistani	Gender	Male	Count	1		1
			Expected Count	1.0		1.0
			% within Gender	100.0%		100.0%
			% within clozapine continuer or discontinuer	50.0%		50.0%
			% of Total	50.0%		50.0%
			Std. Residual	0.0		
		Female	Count	1		1
			Expected Count	1.0		1.0
			% within Gender	100.0%		100.0%
			% within clozapine	50.0%		50.0%

Ethnicity				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			continuer or discontinuer			
			% of Total	50.0%		50.0%
			Std. Residual	0.0		
	Total		Count	2		2
			Expected Count	2.0		2.0
			% within Gender	100.0%		100.0%
			% within clozapine continuer or discontinuer	100.0%		100.0%
			% of Total	100.0%		100.0%
Turkish	Gender	Male	Count		1	1
			Expected Count		1.0	1.0
			% within Gender		100.0%	100.0%
			% within clozapine continuer or discontinuer		100.0%	100.0%
			% of Total		100.0%	100.0%
			Std. Residual		.0	
	Total		Count		1	1
			Expected Count		1.0	1.0
			% within Gender		100.0%	100.0%
			% within clozapine continuer or discontinuer		100.0%	100.0%
			% of Total		100.0%	100.0%
Sri Lankan	Gender	Male	Count		1	1
			Expected Count		1.0	1.0
			% within Gender		100.0%	100.0%
			% within clozapine continuer or discontinuer		100.0%	100.0%
			% of Total		100.0%	100.0%
			Std. Residual		0.0	
	Total		Count		1	1
			Expected Count		1.0	1.0
			% within Gender		100.0%	100.0%
			% within clozapine		100.0%	100.0%

Ethnicity				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			continuer or discontinuer			
			% of Total		100.0%	100.0%
Bangladeshi	Gender	Male	Count	1		1
			Expected Count	1.0		1.0
			% within Gender	100.0%		100.0%
			% within clozapine continuer or discontinuer	100.0%		100.0%
			% of Total	100.0%		100.0%
			Std. Residual	0.0		
	Total		Count	1		1
			Expected Count	1.0		1.0
			% within Gender	100.0%		100.0%
			% within clozapine continuer or discontinuer	100.0%		100.0%
			% of Total	100.0%		100.0%
Other	Gender	Male	Count	1		1
			Expected Count	1.0		1.0
			% within Gender	100.0%		100.0%
			% within clozapine continuer or discontinuer	100.0%		100.0%
			% of Total	100.0%		100.0%
			Std. Residual	0.0		
	Total		Count	1		1
			Expected Count	1.0		1.0
			% within Gender	100.0%		100.0%
			% within clozapine continuer or discontinuer	100.0%		100.0%
			% of Total	100.0%		100.0%
Total	Gender	Male	Count	53_a	40_b	93
			Expected Count	59.4	33.6	93.0
			% within Gender	57.0%	43.0%	100.0%
			% within clozapine continuer or discontinuer	62.4%	83.3%	69.9%

Ethnicity				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			% of Total	39.8%	30.1%	69.9%
			Std. Residual	-0.8	1.1	
		Female	Count	32_a	8_b	40
			Expected Count	25.6	14.4	40.0
			% within Gender	80.0%	20.0%	100.0%
			% within clozapine continuer or discontinuer	37.6%	16.7%	30.1%
			% of Total	24.1%	6.0%	30.1%
			Std. Residual	1.3	-1.7	
	Total		Count	85	48	133
			Expected Count	85.0	48.0	133.0
			% within Gender	63.9%	36.1%	100.0%
			% within clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	63.9%	36.1%	100.0%

Each subscript letter denotes a subset of clozapine continuer or discontinuer categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 7-241 Multiway crosstabulation table, gender x clozapine continuer or discontinuer x diagnosis

Diagnosis				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
F20	Gender	Male	Count	41_a	28_a	69
			Expected Count	44.0	25.0	69.0
			% within Gender	59.4%	40.6%	100.0%
			% within Clozapine continuer or discontinuer	70.7%	84.8%	75.8%
			% of Total	45.1%	30.8%	75.8%
			Std. Residual	-0.4	0.6	
		Female	Count	17_a	5_a	22
			Expected Count	14.0	8.0	22.0
			% within Gender	77.3%	22.7%	100.0%
			% within Clozapine continuer or discontinuer	29.3%	15.2%	24.2%
			% of Total	18.7%	5.5%	24.2%
			Std. Residual	0.8	-1.1	
	Total		Count	58	33	91
			Expected Count	58.0	33.0	91.0
			% within Gender	63.7%	36.3%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	63.7%	36.3%	100.0%
F25	Gender	Male	Count	5_a	6_b	11

			Expected Count	7.2	3.9	11.0
			% within Gender	45.5%	54.5%	100.0%
			% within Clozapine continuer or discontinuer	38.5%	85.7%	55.0%
			% of Total	25.0%	30.0%	55.0%
			Std. Residual	-0.8	1.1	
		Female	Count	8_a	1_b	9
			Expected Count	5.9	3.2	9.0
			% within Gender	88.9%	11.1%	100.0%
			% within Clozapine continuer or discontinuer	61.5%	14.3%	45.0%
			% of Total	40.0%	5.0%	45.0%
			Std. Residual	0.9	-1.2	
	Total		Count	13	7	20
			Expected Count	13.0	7.0	20.0
			% within Gender	65.0%	35.0%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	65.0%	35.0%	100.0%
F31	Gender	Male	Count	2_a	3_a	5
			Expected Count	3.3	1.7	5.0
			% within Gender	40.0%	60.0%	100.0%
			% within Clozapine continuer or discontinuer	33.3%	100.0%	55.6%
			% of Total	22.2%	33.3%	55.6%
			Std. Residual	-0.7	1.0	
		Female	Count	4_a	0_a	4
			Expected Count	2.7	1.3	4.0
			% within Gender	100.0%	0.0%	100.0%
			% within Clozapine continuer or discontinuer	66.7%	0.0%	44.4%
			% of Total	44.4%	0.0%	44.4%
			Std. Residual	0.8	-1.2	
	Total		Count	6	3	9
			Expected Count	6.0	3.0	9.0
			% within Gender	66.7%	33.3%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	66.7%	33.3%	100.0%
Other	Gender	Male	Count	5_a	3_a	8
			Expected Count	4.9	3.1	8.0
			% within Gender	62.5%	37.5%	100.0%
			% within Clozapine continuer or discontinuer	62.5%	60.0%	61.5%
			% of Total	38.5%	23.1%	61.5%
			Std. Residual	0.0	0.0	
		Female	Count	3_a	2_a	5
			Expected Count	3.1	1.9	5.0
			% within Gender	60.0%	40.0%	100.0%

			% within Clozapine continuer or discontinuer	37.5%	40.0%	38.5%
			% of Total	23.1%	15.4%	38.5%
			Std. Residual	0.0	0.1	
	Total		Count	8	5	13
			Expected Count	8.0	5.0	13.0
			% within Gender	61.5%	38.5%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	61.5%	38.5%	100.0%
Total	Gender	Male	Count	53_a	40_b	93
			Expected Count	59.4	33.6	93.0
			% within Gender	57.0%	43.0%	100.0%
			% within Clozapine continuer or discontinuer	62.4%	83.3%	69.9%
			% of Total	39.8%	30.1%	69.9%
			Std. Residual	-0.8	1.1	
		Female	Count	32_a	8_b	40
			Expected Count	25.6	14.4	40.0
			% within Gender	80.0%	20.0%	100.0%
			% within Clozapine continuer or discontinuer	37.6%	16.7%	30.1%
			% of Total	24.1%	6.0%	30.1%
			Std. Residual	1.3	-1.7	
	Total		Count	85	48	133
			Expected Count	85.0	48.0	133.0
			% within Gender	63.9%	36.1%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	63.9%	36.1%	100.0%

Each subscript letter denotes a subset of clozapine continuer or discontinuer categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 7-242 Multiway crosstabulation table, gender x clozapine continuer or discontinuer x merged ethnicity categories

Ethnicity category				**Clozapine continuer or discontinuer**		**Total**
				Continuer	**Discontinuer**	
White	Gender	Male	Count	25_a	16_a	41
			Expected Count	27.6	13.4	41.0
			% within Gender	61.0%	39.0%	100.0%
			% within Clozapine continuer or discontinuer	67.6%	88.9%	74.5%
			% of Total	45.5%	29.1%	74.5%
			Std. Residual	-0.5	0.7	
		Female	Count	12_a	2_a	14
			Expected Count	9.4	4.6	14.0
			% within Gender	85.7%	14.3%	100.0%
			% within Clozapine continuer or discontinuer	32.4%	11.1%	25.5%
			% of Total	21.8%	3.6%	25.5%

Ethnicity category				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			Std. Residual	0.8	-1.2	
	Total		Count	37	18	55
			Expected Count	37.0	18.0	55.0
			% within Gender	67.3%	32.7%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	67.3%	32.7%	100.0%
Black	Gender	Male	Count	18_a	19_a	37
			Expected Count	21.1	15.9	37.0
			% within Gender	48.6%	51.4%	100.0%
			% within Clozapine continuer or discontinuer	56.3%	79.2%	66.1%
			% of Total	32.1%	33.9%	66.1%
			Std. Residual	-0.7	0.8	
		Female	Count	14_a	5_a	19
			Expected Count	10.9	8.1	19.0
			% within Gender	73.7%	26.3%	100.0%
			% within Clozapine continuer or discontinuer	43.8%	20.8%	33.9%
			% of Total	25.0%	8.9%	33.9%
			Std. Residual	1.0	-1.1	
	Total		Count	32	24	56
			Expected Count	32.0	24.0	56.0
			% within Gender	57.1%	42.9%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	57.1%	42.9%	100.0%
Asian	Gender	Male	Count	2_a	3_a	5
			Expected Count	2.8	2.2	5.0
			% within Gender	40.0%	60.0%	100.0%
			% within Clozapine continuer or discontinuer	40.0%	75.0%	55.6%
			% of Total	22.2%	33.3%	55.6%
			Std. Residual	-0.5	0.5	
		Female	Count	3_a	1_a	4
			Expected Count	2.2	1.8	4.0
			% within Gender	75.0%	25.0%	100.0%
			% within Clozapine continuer or discontinuer	60.0%	25.0%	44.4%
			% of Total	33.3%	11.1%	44.4%
			Std. Residual	0.5	-0.6	
	Total		Count	5	4	9
			Expected Count	5.0	4.0	9.0
			% within Gender	55.6%	44.4%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	55.6%	44.4%	100.0%
Mixed	Gender	Male	Count	7_a	1_a	8

Ethnicity category				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			Expected Count	7.2	.8	8.0
			% within Gender	87.5%	12.5%	100.0%
			% within Clozapine continuer or discontinuer	77.8%	100.0%	80.0%
			% of Total	70.0%	10.0%	80.0%
			Std. Residual	-0.1	0.2	
		Female	Count	2_a	0_a	2
			Expected Count	1.8	0.2	2.0
			% within Gender	100.0%	0.0%	100.0%
			% within Clozapine continuer or discontinuer	22.2%	0.0%	20.0%
			% of Total	20.0%	0.0%	20.0%
			Std. Residual	0.1	-0.4	
	Total		Count	9	1	10
			Expected Count	9.0	1.0	10.0
			% within Gender	90.0%	10.0%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	90.0%	10.0%	100.0%
Other	Gender	Male	Count	1_a	1_a	2
			Expected Count	1.3	0.7	2.0
			% within Gender	50.0%	50.0%	100.0%
			% within Clozapine continuer or discontinuer	50.0%	100.0%	66.7%
			% of Total	33.3%	33.3%	66.7%
			Std. Residual	-0.3	0.4	
		Female	Count	1_a	0_a	1
			Expected Count	0.7	0.3	1.0
			% within Gender	100.0%	0.0%	100.0%
			% within Clozapine continuer or discontinuer	50.0%	0.0%	33.3%
			% of Total	33.3%	0.0%	33.3%
			Std. Residual	0.4	-0.6	
	Total		Count	2	1	3
			Expected Count	2.0	1.0	3.0
			% within Gender	66.7%	33.3%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	66.7%	33.3%	100.0%
Total	Gender	Male	Count	53_a	40_b	93
			Expected Count	59.4	33.6	93.0
			% within Gender	57.0%	43.0%	100.0%
			% within Clozapine continuer or discontinuer	62.4%	83.3%	69.9%
			% of Total	39.8%	30.1%	69.9%
			Std. Residual	-0.8	1.1	
		Female	Count	32_a	8_b	40
			Expected Count	25.6	14.4	40.0

Ethnicity category				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			% within Gender	80.0%	20.0%	100.0%
			% within Clozapine continuer or discontinuer	37.6%	16.7%	30.1%
			% of Total	24.1%	6.0%	30.1%
			Std. Residual	1.3	-1.7	
	Total		Count	85	48	133
			Expected Count	85.0	48.0	133.0
			% within Gender	63.9%	36.1%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	63.9%	36.1%	100.0%

Each subscript letter denotes a subset of clozapine continuer or discontinuer categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 7-243 Multiway crosstabulation table, gender x clozapine continuer or discontinuer x merged ethnicity category

Ethnicity category merged				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
White	Gender	Male	Count	25_a	16_a	41
			Expected Count	27.6	13.4	41.0
			% within Gender	61.0%	39.0%	100.0%
			% within Clozapine continuer or discontinuer	67.6%	88.9%	74.5%
			% of Total	45.5%	29.1%	74.5%
			Std. Residual	-0.5	0.7	
		Female	Count	12_a	2_a	14
			Expected Count	9.4	4.6	14.0
			% within Gender	85.7%	14.3%	100.0%
			% within Clozapine continuer or discontinuer	32.4%	11.1%	25.5%
			% of Total	21.8%	3.6%	25.5%
			Std. Residual	0.8	-1.2	
	Total		Count	37	18	55
			Expected Count	37.0	18.0	55.0
			% within Gender	67.3%	32.7%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	67.3%	32.7%	100.0%
Black	Gender	Male	Count	18_a	19_a	37
			Expected Count	21.1	15.9	37.0
			% within Gender	48.6%	51.4%	100.0%
			% within Clozapine continuer or discontinuer	56.3%	79.2%	66.1%
			% of Total	32.1%	33.9%	66.1%
			Std. Residual	-0.7	0.8	
		Female	Count	14_a	5_a	19
			Expected Count	10.9	8.1	19.0
			% within Gender	73.7%	26.3%	100.0%

Ethnicity category merged				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			% within Clozapine continuer or discontinuer	43.8%	20.8%	33.9%
			% of Total	25.0%	8.9%	33.9%
			Std. Residual	1.0	-1.1	
	Total		Count	32	24	56
			Expected Count	32.0	24.0	56.0
			% within Gender	57.1%	42.9%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	57.1%	42.9%	100.0%
Other	Gender	Male	Count	10_a	5_a	15
			Expected Count	10.9	4.1	15.0
			% within Gender	66.7%	33.3%	100.0%
			% within Clozapine continuer or discontinuer	62.5%	83.3%	68.2%
			% of Total	45.5%	22.7%	68.2%
			Std. Residual	-0.3	0.4	
		Female	Count	6_a	1_a	7
			Expected Count	5.1	1.9	7.0
			% within Gender	85.7%	14.3%	100.0%
			% within Clozapine continuer or discontinuer	37.5%	16.7%	31.8%
			% of Total	27.3%	4.5%	31.8%
			Std. Residual	0.4	-0.7	
	Total		Count	16	6	22
			Expected Count	16.0	6.0	22.0
			% within Gender	72.7%	27.3%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	72.7%	27.3%	100.0%
Total	Gender	Male	Count	53_a	40_b	93
			Expected Count	59.4	33.6	93.0
			% within Gender	57.0%	43.0%	100.0%
			% within Clozapine continuer or discontinuer	62.4%	83.3%	69.9%
			% of Total	39.8%	30.1%	69.9%
			Std. Residual	-0.8	1.1	
		Female	Count	32_a	8_b	40
			Expected Count	25.6	14.4	40.0
			% within Gender	80.0%	20.0%	100.0%
			% within Clozapine continuer or discontinuer	37.6%	16.7%	30.1%
			% of Total	24.1%	6.0%	30.1%
			Std. Residual	1.3	-1.7	
	Total		Count	85	48	133
			Expected Count	85.0	48.0	133.0
			% within Gender	63.9%	36.1%	100.0%

Ethnicity category merged			Clozapine continuer or discontinuer		Total
			Continuer	Discontinuer	
		% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
		% of Total	63.9%	36.1%	100.0%

Each subscript letter denotes a subset of clozapine continuer or discontinuer categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 7-244 Multiway crosstabulation table, gender x clozapine continuer or discontinuer x merged diagnosis category

Diagnosis category				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
F20	Gender	Male	Count	41_a	28_a	69
			Expected Count	44.0	25.0	69.0
			% within Gender	59.4%	40.6%	100.0%
			% within Clozapine continuer or discontinuer	70.7%	84.8%	75.8%
			% of Total	45.1%	30.8%	75.8%
			Std. Residual	-0.4	0.6	
		Female	Count	17_a	5_a	22
			Expected Count	14.0	8.0	22.0
			% within Gender	77.3%	22.7%	100.0%
			% within Clozapine continuer or discontinuer	29.3%	15.2%	24.2%
			% of Total	18.7%	5.5%	24.2%
			Std. Residual	0.8	-1.1	
	Total		Count	58	33	91
			Expected Count	58.0	33.0	91.0
			% within Gender	63.7%	36.3%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	63.7%	36.3%	100.0%
F25	Gender	Male	Count	5_a	6_b	11
			Expected Count	7.2	3.9	11.0
			% within Gender	45.5%	54.5%	100.0%
			% within Clozapine continuer or discontinuer	38.5%	85.7%	55.0%
			% of Total	25.0%	30.0%	55.0%
			Std. Residual	-0.8	1.1	
		Female	Count	8_a	1_b	9
			Expected Count	5.9	3.2	9.0
			% within Gender	88.9%	11.1%	100.0%
			% within Clozapine continuer or discontinuer	61.5%	14.3%	45.0%
			% of Total	40.0%	5.0%	45.0%
			Std. Residual	0.9	-1.2	
	Total		Count	13	7	20
			Expected Count	13.0	7.0	20.0
			% within Gender	65.0%	35.0%	100.0%

Diagnosis category				Clozapine continuer or discontinuer		Total
				Continuer	Discontinuer	
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	65.0%	35.0%	100.0%
Other	Gender	Male	Count	7_a	6_a	13
			Expected Count	8.3	4.7	13.0
			% within Gender	53.8%	46.2%	100.0%
			% within Clozapine continuer or discontinuer	50.0%	75.0%	59.1%
			% of Total	31.8%	27.3%	59.1%
			Std. Residual	-0.4	0.6	
		Female	Count	7_a	2_a	9
			Expected Count	5.7	3.3	9.0
			% within Gender	77.8%	22.2%	100.0%
			% within Clozapine continuer or discontinuer	50.0%	25.0%	40.9%
			% of Total	31.8%	9.1%	40.9%
			Std. Residual	0.5	-0.7	
	Total		Count	14	8	22
			Expected Count	14.0	8.0	22.0
			% within Gender	63.6%	36.4%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	63.6%	36.4%	100.0%
Total	Gender	Male	Count	53_a	40_b	93
			Expected Count	59.4	33.6	93.0
			% within Gender	57.0%	43.0%	100.0%
			% within Clozapine continuer or discontinuer	62.4%	83.3%	69.9%
			% of Total	39.8%	30.1%	69.9%
			Std. Residual	-0.8	1.1	
		Female	Count	32_a	8_b	40
			Expected Count	25.6	14.4	40.0
			% within Gender	80.0%	20.0%	100.0%
			% within Clozapine continuer or discontinuer	37.6%	16.7%	30.1%
			% of Total	24.1%	6.0%	30.1%
			Std. Residual	1.3	-1.7	
	Total		Count	85	48	133
			Expected Count	85.0	48.0	133.0
			% within Gender	63.9%	36.1%	100.0%
			% within Clozapine continuer or discontinuer	100.0%	100.0%	100.0%
			% of Total	63.9%	36.1%	100.0%

Each subscript letter denotes a subset of clozapine continuer or discontinuer categories whose column proportions do not differ significantly from each other at the 0.05 level.

Table 7-245 Logistic regression iteration history, gender

Iteration		-2 Log likelihood	Coefficients
			Constant
Step 0	1	173.954	-0.556
	2	173.947	-0.571
	3	173.947	-0.571

Table 7-246 Logistic regression summary statistics

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	167.134	0.050	0.068

Table 7-247 Logistic regression classification table

Observed		Predicted		
		Clozapine continuer or discontinuer		Percentage Correct
		Continuer	Discontinuer	
Clozapine continuer or discontinuer	Continuer	85	0	100.0
	Discontinuer	48	0	0.0
Overall Percentage				63.9

Table 7-248 Logistic regression equation variables

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
Male	1.105	0.447	6.100	1	0.014	3.019	1.256	7.255
Constant	-1.386	0.395	12.300	1	<0.0005	0.250		

Table 7-249 Logistic regression bootstrap

	b	Bootstrap				
		Bias	Std. Error	Sig. (2-tailed)	95% Confidence Interval	
					Lower	Upper
Male	1.105	0.033	0.476	0.010	0.235	2.138
Constant	-1.386	-0.030	0.417	0.001	-2.398	-0.694

Table 7-250 Table of residuals

			Case Number	Predicted probability	Predicted group	Analog of Cook's influence statistics	Leverage value	Normalized residual	DFBETA for constant	DFBETA for male
Gender	Male	1	5	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		2	6	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		3	7	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		4	8	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		5	10	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		6	14	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		7	17	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		8	18	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		9	19	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		10	21	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		11	22	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		12	25	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		13	26	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		14	32	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		15	33	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		16	34	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		17	35	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		18	36	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		19	41	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		20	42	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		21	43	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		22	44	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		23	47	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		24	48	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		25	51	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		26	52	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		27	53	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		28	54	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		29	55	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		30	56	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		31	57	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		32	59	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		33	62	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907

			Case Number	Predicted probability	Predicted group	Analog of Cook's influence statistics	Leverage value	Normalized residual	DFBETA for constant	DFBETA for male
		34	63	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		35	64	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		36	65	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		37	66	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		38	68	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		39	69	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		40	70	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		41	71	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		42	73	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		43	74	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		44	75	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		45	76	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		46	77	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		47	79	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		48	80	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		49	81	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		50	82	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		51	83	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		52	84	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		53	85	0.43011	Continuer	0.00820	0.01075	-0.86874	<0.000005	-0.01907
		54	87	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		55	90	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		56	91	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		57	92	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		58	93	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		59	94	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		60	95	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		61	96	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		62	97	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		63	98	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		64	99	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		65	100	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		66	102	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		67	104	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527

			Case Number	Predicted probability	Predicted group	Analog of Cook's influence statistics	Leverage value	Normalized residual	DFBETA for constant	DFBETA for male
		68	105	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		69	106	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		70	107	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		71	108	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		72	110	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		73	111	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		74	112	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		75	113	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		76	114	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		77	116	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		78	117	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		79	119	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		80	120	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		81	121	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		82	122	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		83	123	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		84	124	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		85	125	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		86	126	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		87	127	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		88	128	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		89	129	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		90	130	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		91	131	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		92	132	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		93	133	0.43011	Continuer	0.01440	0.01075	1.15109	<0.000005	0.02527
		Total | *n*		93	93	93	93	93	93	93
	Female	1	1	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		2	2	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		3	3	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		4	4	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		5	9	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		6	11	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		7	12	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205

			Case Number	Predicted probability	Predicted group	Analog of Cook's influence statistics	Leverage value	Normalized residual	DFBETA for constant	DFBETA for male
		8	13	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		9	15	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		10	16	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		11	20	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		12	23	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		13	24	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		14	27	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		15	28	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		16	29	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		17	30	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		18	31	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		19	37	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		20	38	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		21	39	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		22	40	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		23	45	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		24	46	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		25	49	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		26	50	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		27	58	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		28	60	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		29	61	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		30	67	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		31	72	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		32	78	0.20000	Continuer	0.00641	0.02500	-0.50000	-0.03205	0.03205
		33	86	0.20000	Continuer	0.10256	0.02500	2.00000	0.12821	-0.12821
		34	88	0.20000	Continuer	0.10256	0.02500	2.00000	0.12821	-0.12821
		35	89	0.20000	Continuer	0.10256	0.02500	2.00000	0.12821	-0.12821
		36	101	0.20000	Continuer	0.10256	0.02500	2.00000	0.12821	-0.12821
		37	103	0.20000	Continuer	0.10256	0.02500	2.00000	0.12821	-0.12821
		38	109	0.20000	Continuer	0.10256	0.02500	2.00000	0.12821	-0.12821
		39	115	0.20000	Continuer	0.10256	0.02500	2.00000	0.12821	-0.12821
		40	118	0.20000	Continuer	0.10256	0.02500	2.00000	0.12821	-0.12821
		Total *n*		40	40	40	40	40	40	40

			Case Number	Predicted probability	Predicted group	Analog of Cook's influence statistics	Leverage value	Normalized residual	DFBETA for constant	DFBETA for male
	Total	*N*		133	133	133	133	133	133	133

Table 7-251 Kaplan-Meier survival table

	Time (days)	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
			Estimate	Std. Error		
1	1.000	Discontinued	0.992	0.007	1	132
2	33.000	Discontinued	0.985	0.011	2	131
3	68.000	Discontinued	0.977	0.013	3	130
4	84.000	Discontinued	0.970	0.015	4	129
5	92.000	Discontinued	0.962	0.016	5	128
6	170.000	Discontinued	0.955	0.018	6	127
7	182.000	Discontinued	0.947	0.019	7	126
8	197.000	Discontinued	0.940	0.021	8	125
9	203.000	Discontinued	0.932	0.022	9	124
10	207.000	Discontinued	0.925	0.023	10	123
11	229.000	Discontinued	0.917	0.024	11	122
12	282.000	Discontinued	0.910	0.025	12	121
13	367.000	Discontinued	0.902	0.026	13	120
14	554.000	Discontinued	0.895	0.027	14	119
15	565.000	Discontinued	0.887	0.027	15	118
16	582.000	Discontinued	0.880	0.028	16	117
17	584.000	Discontinued	0.872	0.029	17	116
18	703.000	Discontinued	0.865	0.030	18	115
19	789.000	Discontinued	0.857	0.030	19	114
20	827.000	Discontinued	0.850	0.031	20	113
21	833.000	Discontinued	0.842	0.032	21	112
22	869.000	Discontinued	0.835	0.032	22	111
23	933.000	Discontinued	0.827	0.033	23	110
24	1012.000	Discontinued	0.820	0.033	24	109
25	1064.000	Discontinued	0.812	0.034	25	108
26	1120.000	Discontinued	0.805	0.034	26	107
27	1146.000	Discontinued	0.797	0.035	27	106
28	1160.000	Discontinued	0.789	0.035	28	105
29	1162.000	Discontinued	0.782	0.036	29	104
30	1215.000	Discontinued	0.774	0.036	30	103
31	1244.000	Discontinued	0.767	0.037	31	102
32	1266.000	Discontinued	0.759	0.037	32	101
33	1339.000	Discontinued	0.752	0.037	33	100
34	1421.000	Discontinued	0.744	0.038	34	99
35	1443.000	Discontinued	0.737	0.038	35	98
36	1457.000	Discontinued	0.729	0.039	36	97
37	1468.000	Discontinued	0.722	0.039	37	96
38	1610.000	Discontinued	0.714	0.039	38	95
39	1739.000	Discontinued	0.707	0.039	39	94
40	1774.000	Censored	.	.	39	93
41	1782.000	Censored	.	.	39	92
42	1783.000	Discontinued	0.699	0.040	40	91
43	1794.000	Censored	.	.	40	90
44	1827.000	Censored	.	.	40	89
45	1839.000	Censored	.	.	40	88
46	1849.000	Censored	.	.	40	87
47	1863.000	Censored	.	.	40	86
48	1865.000	Censored	.	.	40	85
49	1865.000	Censored	.	.	40	84
50	1866.000	Discontinued	0.691	0.040	41	83
51	1870.000	Censored	.	.	41	82
52	1905.000	Censored	.	.	41	81
53	1974.000	Discontinued	0.682	0.041	42	80
54	1989.000	Censored	.	.	42	79

	Time (days)	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
			Estimate	Std. Error		
55	2019.000	Censored	.	.	42	78
56	2020.000	Censored	.	.	42	77
57	2034.000	Censored	.	.	42	76
58	2041.000	Censored	.	.	42	75
59	2056.000	Discontinued	0.673	0.041	43	74
60	2108.000	Censored	.	.	43	73
61	2129.000	Censored	.	.	43	72
62	2146.000	Censored	.	.	43	71
63	2147.000	Censored	.	.	43	70
64	2153.000	Censored	.	.	43	69
65	2158.000	Censored	.	.	43	68
66	2160.000	Censored	.	.	43	67
67	2167.000	Censored	.	.	43	66
68	2172.000	Discontinued	0.663	0.042	44	65
69	2187.000	Censored	.	.	44	64
70	2188.000	Discontinued	0.653	0.042	45	63
71	2201.000	Censored	.	.	45	62
72	2221.000	Censored	.	.	45	61
73	2238.000	Censored	.	.	45	60
74	2299.000	Discontinued	0.642	0.043	46	59
75	2308.000	Censored	.	.	46	58
76	2312.000	Censored	.	.	46	57
77	2315.000	Censored	.	.	46	56
78	2330.000	Censored	.	.	46	55
79	2360.000	Censored	.	.	46	54
80	2396.000	Censored	.	.	46	53
81	2404.000	Censored	.	.	46	52
82	2429.000	Censored	.	.	46	51
83	2437.000	Censored	.	.	46	50
84	2450.000	Censored	.	.	46	49
85	2472.000	Discontinued	0.629	0.044	47	48
86	2480.000	Censored	.	.	47	47
87	2482.000	Censored	.	.	47	46
88	2521.000	Censored	.	.	47	45
89	2524.000	Discontinued	0.615	0.045	48	44
90	2536.000	Censored	.	.	48	43
91	2538.000	Censored	.	.	48	42
92	2539.000	Censored	.	.	48	41
93	2574.000	Censored	.	.	48	40
94	2591.000	Censored	.	.	48	39
95	2599.000	Censored	.	.	48	38
96	2606.000	Censored	.	.	48	37
97	2608.000	Censored	.	.	48	36
98	2609.000	Censored	.	.	48	35
99	2622.000	Censored	.	.	48	34
100	2634.000	Censored	.	.	48	33
101	2682.000	Censored	.	.	48	32
102	2693.000	Censored	.	.	48	31
103	2706.000	Censored	.	.	48	30
104	2717.000	Censored	.	.	48	29
105	2774.000	Censored	.	.	48	28
106	2788.000	Censored	.	.	48	27
107	2816.000	Censored	.	.	48	26
108	2816.000	Censored	.	.	48	25
109	2829.000	Censored	.	.	48	24

	Time (days)	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
			Estimate	Std. Error		
110	2832.000	Censored	.	.	48	23
111	2836.000	Censored	.	.	48	22
112	2844.000	Censored	.	.	48	21
113	2859.000	Censored	.	.	48	20
114	2860.000	Censored	.	.	48	19
115	2880.000	Censored	.	.	48	18
116	2908.000	Censored	.	.	48	17
117	2924.000	Censored	.	.	48	16
118	2928.000	Censored	.	.	48	15
119	2951.000	Censored	.	.	48	14
120	2955.000	Censored	.	.	48	13
121	2990.000	Censored	.	.	48	12
122	3000.000	Censored	.	.	48	11
123	3018.000	Censored	.	.	48	10
124	3031.000	Censored	.	.	48	9
125	3031.000	Censored	.	.	48	8
126	3035.000	Censored	.	.	48	7
127	3061.000	Censored	.	.	48	6
128	3069.000	Censored	.	.	48	5
129	3092.000	Censored	.	.	48	4
130	3118.000	Censored	.	.	48	3
131	3148.000	Censored	.	.	48	2
132	3200.000	Censored	.	.	48	1
133	3207.000	Censored	.	.	48	0

Table 7-252 Kaplan-Meier survival analysis, gender case summary

Gender	Total N	N of Events	Censored	
			N	Percent
Male	93	40	53	57.0%
Female	40	8	32	80.0%
Overall	133	48	85	63.9%

Table 7-253 Kaplan-Meier survival table, separated for gender

Gender		Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
				Estimate	Std. Error		
Male	1	1.000	Discontinued	0.989	0.011	1	92
	2	33.000	Discontinued	0.978	0.015	2	91
	3	68.000	Discontinued	0.968	0.018	3	90
	4	84.000	Discontinued	0.957	0.021	4	89
	5	92.000	Discontinued	0.946	0.023	5	88
	6	170.000	Discontinued	0.935	0.025	6	87
	7	182.000	Discontinued	0.925	0.027	7	86
	8	197.000	Discontinued	0.914	0.029	8	85
	9	203.000	Discontinued	0.903	0.031	9	84
	10	229.000	Discontinued	0.892	0.032	10	83
	11	282.000	Discontinued	0.882	0.033	11	82
	12	554.000	Discontinued	0.871	0.035	12	81
	13	582.000	Discontinued	0.860	0.036	13	80
	14	584.000	Discontinued	0.849	0.037	14	79
	15	703.000	Discontinued	0.839	0.038	15	78
	16	789.000	Discontinued	0.828	0.039	16	77

Gender		Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
				Estimate	Std. Error		
	17	827.000	Discontinued	0.817	0.040	17	76
	18	833.000	Discontinued	0.806	0.041	18	75
	19	933.000	Discontinued	0.796	0.042	19	74
	20	1012.000	Discontinued	0.785	0.043	20	73
	21	1064.000	Discontinued	0.774	0.043	21	72
	22	1120.000	Discontinued	0.763	0.044	22	71
	23	1146.000	Discontinued	0.753	0.045	23	70
	24	1160.000	Discontinued	0.742	0.045	24	69
	25	1215.000	Discontinued	0.731	0.046	25	68
	26	1244.000	Discontinued	0.720	0.047	26	67
	27	1266.000	Discontinued	0.710	0.047	27	66
	28	1339.000	Discontinued	0.699	0.048	28	65
	29	1421.000	Discontinued	0.688	0.048	29	64
	30	1443.000	Discontinued	0.677	0.048	30	63
	31	1457.000	Discontinued	0.667	0.049	31	62
	32	1468.000	Discontinued	0.656	0.049	32	61
	33	1610.000	Discontinued	0.645	0.050	33	60
	34	1739.000	Discontinued	0.634	0.050	34	59
	35	1774.000	Censored	.	.	34	58
	36	1783.000	Discontinued	0.623	0.050	35	57
	37	1794.000	Censored	.	.	35	56
	38	1827.000	Censored	.	.	35	55
	39	1863.000	Censored	.	.	35	54
	40	1865.000	Censored	.	.	35	53
	41	1866.000	Discontinued	0.612	0.051	36	52
	42	1905.000	Censored	.	.	36	51
	43	1974.000	Discontinued	0.600	0.051	37	50
	44	2019.000	Censored	.	.	37	49
	45	2020.000	Censored	.	.	37	48
	46	2034.000	Censored	.	.	37	47
	47	2041.000	Censored	.	.	37	46
	48	2056.000	Discontinued	0.587	0.052	38	45
	49	2108.000	Censored	.	.	38	44
	50	2129.000	Censored	.	.	38	43
	51	2146.000	Censored	.	.	38	42
	52	2147.000	Censored	.	.	38	41
	53	2153.000	Censored	.	.	38	40
	54	2158.000	Censored	.	.	38	39
	55	2160.000	Censored	.	.	38	38
	56	2172.000	Discontinued	0.571	0.053	39	37
	57	2187.000	Censored	.	.	39	36
	58	2201.000	Censored	.	.	39	35
	59	2312.000	Censored	.	.	39	34
	60	2315.000	Censored	.	.	39	33
	61	2360.000	Censored	.	.	39	32
	62	2437.000	Censored	.	.	39	31
	63	2450.000	Censored	.	.	39	30
	64	2482.000	Censored	.	.	39	29
	65	2524.000	Discontinued	0.552	0.054	40	28
	66	2536.000	Censored	.	.	40	27
	67	2539.000	Censored	.	.	40	26
	68	2574.000	Censored	.	.	40	25

Gender		Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
				Estimate	Std. Error		
	69	2599.000	Censored	.	.	40	24
	70	2608.000	Censored	.	.	40	23
	71	2609.000	Censored	.	.	40	22
	72	2634.000	Censored	.	.	40	21
	73	2682.000	Censored	.	.	40	20
	74	2693.000	Censored	.	.	40	19
	75	2706.000	Censored	.	.	40	18
	76	2717.000	Censored	.	.	40	17
	77	2774.000	Censored	.	.	40	16
	78	2788.000	Censored	.	.	40	15
	79	2816.000	Censored	.	.	40	14
	80	2829.000	Censored	.	.	40	13
	81	2836.000	Censored	.	.	40	12
	82	2844.000	Censored	.	.	40	11
	83	2860.000	Censored	.	.	40	10
	84	2924.000	Censored	.	.	40	9
	85	2928.000	Censored	.	.	40	8
	86	2951.000	Censored	.	.	40	7
	87	2955.000	Censored	.	.	40	6
	88	3000.000	Censored	.	.	40	5
	89	3018.000	Censored	.	.	40	4
	90	3031.000	Censored	.	.	40	3
	91	3061.000	Censored	.	.	40	2
	92	3069.000	Censored	.	.	40	1
	93	3092.000	Censored	.	.	40	0
Female	1	207.000	Discontinued	0.975	0.025	1	39
	2	367.000	Discontinued	0.950	0.034	2	38
	3	565.000	Discontinued	0.925	0.042	3	37
	4	869.000	Discontinued	0.900	0.047	4	36
	5	1162.000	Discontinued	0.875	0.052	5	35
	6	1782.000	Censored	.	.	5	34
	7	1839.000	Censored	.	.	5	33
	8	1849.000	Censored	.	.	5	32
	9	1865.000	Censored	.	.	5	31
	10	1870.000	Censored	.	.	5	30
	11	1989.000	Censored	.	.	5	29
	12	2167.000	Censored	.	.	5	28
	13	2188.000	Discontinued	0.844	0.059	6	27
	14	2221.000	Censored	.	.	6	26
	15	2238.000	Censored	.	.	6	25
	16	2299.000	Discontinued	0.810	0.066	7	24
	17	2308.000	Censored	.	.	7	23
	18	2330.000	Censored	.	.	7	22
	19	2396.000	Censored	.	.	7	21
	20	2404.000	Censored	.	.	7	20
	21	2429.000	Censored	.	.	7	19
	22	2472.000	Discontinued	0.767	0.075	8	18
	23	2480.000	Censored	.	.	8	17
	24	2521.000	Censored	.	.	8	16
	25	2538.000	Censored	.	.	8	15
	26	2591.000	Censored	.	.	8	14
	27	2606.000	Censored	.	.	8	13

Gender		Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
				Estimate	Std. Error		
	28	2622.000	Censored	.	.	8	12
	29	2816.000	Censored	.	.	8	11
	30	2832.000	Censored	.	.	8	10
	31	2859.000	Censored	.	.	8	9
	32	2880.000	Censored	.	.	8	8
	33	2908.000	Censored	.	.	8	7
	34	2990.000	Censored	.	.	8	6
	35	3031.000	Censored	.	.	8	5
	36	3035.000	Censored	.	.	8	4
	37	3118.000	Censored	.	.	8	3
	38	3148.000	Censored	.	.	8	2
	39	3200.000	Censored	.	.	8	1
	40	3207.000	Censored	.	.	8	0

Table 7-254 Risk estimate for discontinuing clozapine

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Gender (Male / Female)	0.331	0.138	0.796
For cohort Continuer = Continuer	0.712	0.563	0.901
For cohort Continuer = Discontinuer	2.151	1.109	4.171
N of Valid Cases	133		

Table 7-255 Chi-square for clozapine discontinuation risk estimate

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	6.421	1	0.011		
Continuity Correction	5.462	1	0.019		
Likelihood Ratio	6.812	1	0.009		
Fisher's Exact Test				0.011	0.008
Linear-by-Linear Association	6.373	1	0.012		
N of Valid Cases	133				

Appendix I. Publications arising from this thesis